THE GENERAL PRACTITIONER AND THE HOSPITAL

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IN the 18th century all doctors were general practitioners. As the surgeon could not open the abdomen, he had plenty of time to practise medicine as well. Hospitals at that time were merely a refuge for the sick poor, with a high mortality from infectious disease and little to offer in the way of treatment. By 1880, however, Lister's antiseptic surgery had been accepted and anæsthesia was firmly established [1]; the picture of the teaching hospital as a medical scientific centre emerged, and the era of specialisation had begun.

Since then the prestige of the hospitals has been such that to be a member of their staff was enough to gain the confidence of the public and of other doctors, leading to lucrative consultant practice. Thus the material advancement of the consultant has depended on his academic and professional achievement.

Industrialisation and the Practitioner

In cities and densely populated industrial districts in Great Britain the separation of hospital and general practice became more and more complete as industrialisation advanced. The general practitioner in working-class areas discovered the well-tried business principle of small profits with a big turnover where the population was large: and growing rapidly, it paid to treat a great many people for a small fee. A waiting-room crammed with patients, each representing 2*s*. 6*d*. for a consultation or 3*s*. 6*d*. if this was consummated by the provision of a bottle of medicine, not only gave a satisfactory income but also reduced the inclination to practise clinical medicine with skilful care, to attend clinical meetings, or to seek refreshment from the scientific literature.

Particularly in coalmining areas, workers formed themselves into clubs to which they contributed a few pence a week, and thus secured free treatment from the club doctor for illness or accident. The club system was the forerunner of health insurance and was a humane and desirable social development. But, like the "cash surgery", it encouraged the doctor to undertake the treatment of more patients than he could deal with efficiently. It also created a difference between the club patients and those who could afford to pay for medical attention. The private patient almost inevitably received, if not better treatment, certainly more consideration of his time and comfort—a difference which was perpetuated when National Health Insurance was eventually introduced.

When the State became responsible, in 1911, for providing a general-practitioner service for insured workers, the system already established was crystallised. The assurance that a doctor's practice was not too large with 2000 panel patients was accepted, and it was not surprising that the fee paid by the State should be related to the fee which the doctor was already accustomed to charge. Thus the principle of small profits and a large turnover received official sanction, and it became even more important with the introduction of the National Health Service in 1948. The rejection by the profession in 1948 of the offer of a basic salary supplemented by a capitation fee—a decision which many general practitioners now bitterly regret—and the insistence on remuneration by capitation fee only, made the size of the practice all-important, as it was in the days of the "cash surgery".

The influence of industrialisation thus set the general practitioner professionally on a path exactly opposite to that of the consultant. Whereas the prosperity of the consultant depended on his being appointed to the staff of a teaching or voluntary hospital and on his clinical success, the prosperity of the general practitioner depended on his ability to attract patients. Admittedly this might, at first depend on his skill as a doctor, but as his practice grew it became harder for him to maintain his standards, and he could not, as the consultant could, increase his fees to discourage an excessive number of patients. A doctor was bound to attend the sick when necessary, and a small fee was better than no fee at all. That practices in poor districts should be large was a natural corollary. Indeed in these circumstances it is a tribute to the profession that its standards in industrial practices were as high as they were.

If criticism is necessary, it should not be of the doctors who developed large industrial practices but of the leaders of all branches of the profession, who did not see the trend of general practice, or, having seen it, did nothing to influence it. It is particularly regrettable that the revolutionary conception of a National Health Service, which has transformed the hospitals of the United Kingdom to the great benefit of the community, should not have brought an equally radical change in general practice. Instead, because of the shortsightedness of the profession, the N.H.S. has preserved and intensified the worst features of general practice, which had their origin in the Industrial Revolution.

General Practice in the Country

In the country, however, and in the smaller towns, general practice followed a very different course. Patients in country practices were more representative of all sections of the community and many could be charged fees which made the necessity for large numbers less compelling than in the cities. The custom of establishing cottage hospitals in smaller towns became widespread in Great Britain towards the end of the 19th century, and these were staffed by general practitioners, many of whom showed a high degree of specialised skill, particularly in surgery and obstetrics. In addition, a healthy tendency soon became apparent towards the formation of group practices with several partners.

In these practices a reasonable division of work was possible, with the result that the doctors had enough leisure to follow special interests. Often they had experience of, or higher qualifications in, surgery, medicine, obstetrics, or radiology, with much benefit to their patients and to the local hospitals. To prepare themselves for this type of practice, the newly qualified had to have wide hospital experience, and the larger hospitals had the benefit of their services during training.

1. Guthrie, D. A History of Medicine. London, 1945.

After 1948

At the beginning of the N.H.S., general practitioners who were specialist members of hospital staffs were obliged to choose between their specialty and their practice, and the break between the hospitals and the general practitioner thus become virtually complete. Because of administrative necessity, the service relegated doctors to well-defined spheres of activity, as far as their relation with specialties was concerned, and for this reason many doctors blame it for lowering the status of general practice. But the damage had been done long before. By past acceptance of the principle of a big turnover and small profits, and by insistence on a capitation fee, the place of the general practitioner in the N.H.S. was inevitably and precisely determined.

By a coincidence the service was introduced at a time of exceptional development in medical science. Not only was the general practitioner in the hospital a relic of the previous era of medicine, but subdivisions also appeared within the ranks of the specialists themselves. Though there are dangers in narrow specialisation, there is also an inevitability about it. Discussing the growing complexity of the curricula of Cambridge University, Sir Arthur Quiller-Couch [2] spoke of "one compelling and obvious cause—the increased and increasing unwieldiness of knowledge". The general practitioner of the N.H.S. is in fact much more a victim of scientific evolution than of the Civil Servant.

The Future

One result of the "disillusionment" of the general practitioner is that sometimes he does not feel that he need be a good doctor to be successful in general practice. The capitation fee covers any service to a patient, and, with a fully equipped hospital nearby, and incidentally with an increasingly litigious public, it is natural that he should refer to hospital many cases which formerly he would have treated himself. A pleasant personality and some attention to the dictum that the customer is always right can ensure a large practice without a sound knowledge of medicine, and the consultant is always close at hand if danger threatens. Only in midwifery does the practitioner retain most of his former functions, and even here the tendency is towards more and more hospital confinements.

The remarks of disgruntled practitioners are always louder than those of contented ones, and phrases like "Medicine has gone to the dogs", "I'm just a glorified clerk", and "I'll take care that my son doesn't become a doctor" are not only broadcast but are widely believed. Unfortunately once an impression is created that general practice has become an inferior occupation, there will be fewer medical students, and an increased proportion of those who qualify will want either to specialise or to emigrate to countries where general practice still presents the picture which they have conceived of it. The remainder who wish to enter general practice in this country will leave hospital at the end of their compulsory year so that they can quickly begin to build up the long list of patients on which their prosperity will depend.

Apart from the necessity for finding junior hospital staff, the work of the hospital itself is impaired by dissatisfied general practitioners, since they are inclined to flood the hospitals with patients who could be treated in surgeries or in their own homes. Relations between the hospital and family doctors are strained because the specialists feel that they are being exploited.

Clinical medicine must be seen as an indivisible whole, and a hospital service depends for its health on a healthy general-practitioner service.

Some Possible Remedies

The general practitioner himself feels that all that is needed is to allow him to return to the hospital. Indeed that view has also been expressed by official bodies. Thus a report from the Department of Health for Scotland (1952) [3] suggests that general-practitioner wards or blocks should be associated with general hospitals, and that in suitable areas general-practitioner hospitals should be provided. "These hospitals would be larger than the average cottage hospitals but in their equipment and in the facilities they would provide they would be less elaborate than the specialist hospitals."

It is hard, however, to see what purpose exactly these hospitals would serve. If admission to hospital is necessary, this is usually because patients need the elaborate facilities which a hospital can provide. There seems to be little point, therefore, in sending them to a general-practitioner hospital unless elementary nursing care cannot be given at home; and the patients to whom this proviso commonly applies are the elderly and the chronic sick. The status of general practitioners is not likely to be altered substantially merely by enabling them to say that they belong to a hospital staff. After all, it was increasing specialisation, not lack of hospital beds, which excluded them from hospitals in the first place, and the process cannot be reversed simply by a building programme.

If the best type of general practice is to be encouraged, the following measures seem to be necessary:

1. A system of remuneration must be devised which will make large practices relatively unprofitable and which will stimulate the formation of partnerships and group practices. Some departure from the capitation-fee principle is clearly indicated and should be combined with a financial incentive towards a high standard of academic qualification for general practice.

2. The general hospitals should become centres of medical education for their districts. If the scheme were pursued with sufficient enthusiasm by the local consultants, doctors who did not take part in it would soon find that they were working in isolation, and the herd instinct might ensure their participation. Further, more intimate association between doctors which the teaching system would create would help to promote friendly professional unity.

3. Diagnostic assistance should be freely available. Although the surgical field of the family doctor has become limited, it is more necessary than ever that he should be highly skilled in diagnosis and as a clinician. How far he can go in this direction, however, depends largely on whether he can investigate his patients as they would be investigated in hospital.

4. The preventive work of the general practitioner should be developed. With his unique experience of his patients as members of families and with his knowledge of their environment, he ought to be particularly fitted both to assess social factors in illness and to protect his patients where protection can be given.

We must remember always that the general practitioner is the only doctor who can offer a personal service to all his patients, whatever their disability may be.

2 Quiller-Couch, A. T. On the Art of Reading. London, 1920.

3. Department of Health for Scotland: Scottish Health Services Council. The General Practitioner and the Hospital Service. H.M. Stationery Office, 1952.

Conclusion

Nobody would dispute that both general practitioners and hospital doctors are necessary. What is disputed, however, is the relative importance of the two kinds of doctors.

With the march of medical science there has been a tendency to glorify the specialist at the expense of the "jack-of-all-trades". But the family doctor is now more important than he has ever been: scientific progress has increased, not diminished his responsibilities.

Those who practise clinical medicine, in the hospital or in the home, make up a team, the members of which depend upon each other for the success of their joint efforts. Different members of the team have different functions, but the importance of each is equal and a weakness in one is a weakness in all.

The Royal Commission did not recommend any change in the system of paying general practitioners by capitation fee. Responsibility for improving general practice, therefore, has been returned to the profession and to the bodies which administer the National Health Service. Now that the financial argument has ended and is unlikely to be renewed, perhaps a great constructive effort can be made to set our house completely in order?

THE SECRETORY BACKGROUND TO GASTRIC ULCER

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MOST patients with duodenal ulcer differ from normal in secreting large quantities of acid at a high concentration. By contrast, the secretory behaviour of patients with gastric ulcer is less uniform, and may differ according to sex and to the site of ulceration within the stomach. Kay (1953) found that men with gastric ulcer attained on average a greater limiting rate of secretion of hydrochloric acid in response to histamine than normal men. Marks and Shay (1959), investigating patients of both sexes, failed to confirm this finding, except for patients with ulcers in the pyloric antrum.

Patients with gastric ulcer also differ among themselves in the acidity of their gastric contents at night. In a majority of cases samples taken after the stomach is empty of food are neutral or slightly alkaline; a minority behave normally in continuing to have acid gastric contents at this time (James and Pickering 1949, Watkinson 1951, Chandler and Watkinson 1959). This difference, too, may depend upon the site of ulceration (Watkinson 1951).

This paper describes an investigation of the secretory behaviour of patients with gastric ulcer, using nocturnal sampling followed by measurement of the response to a large dose of histamine. The purpose was to find out whether the different responses to histamine and the differences in acidity at night were the result of variations in one or in more than one physiological function.

Material

There were 50 patients, of whom 29 were men and 21 were women. Their ages varied between 22 and 82, and the period that had elapsed since their first remembered dyspepsia from six weeks to forty years. All of them had been shown to have an ulcer crater in the stomach four weeks or less before the investigation, had a hæmoglobin concentration greater than

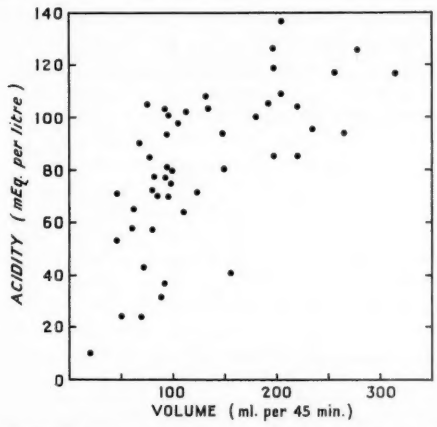

Fig. 1—Relation between volume and acidity of gastric secretion after histamine (0·4 mg. per 10 kg. body-weight) in 50 patients with gastric ulcer.

11·1 g. per 100 ml. (75% Haldane), and had not recently bled. 10 of the men and 5 of the women also showed radiological evidence of chronic duodenal ulceration, the activity of which could not be assessed. The sites of the gastric ulcers were decided by inspection of the X-ray films. An ulcer was defined as antral when the crater was below a line drawn horizontally from the incisura, "incisural" when it lay wholly or partly between this line and another drawn 1 in. (2·5 cm.) above it, and in the body of the stomach when it was above the upper of the two lines.

Methods

The contents of the patients' stomachs were sampled at intervals through the night, and on the next morning their gastric secretion was collected after a single large dose of histamine (0·4 mg. per 10 kg. body-weight).

Sampling was carried out every half-hour from 8.30 P.M. until 7.30 A.M.; otherwise the methods used were those described by James and Pickering (1949). The pH of the samples was measured with the glass electrode; the estimations were accurate to within 0·1 pH unit. No precautions were taken to prevent loss of carbon dioxide. In samples which did not contain food the chloride concentration was measured by the method of Sanderson (1952); the few samples in which it was less than 120 mEq. per litre were excluded as being contaminated with saliva. Bile staining occurred infrequently and made little difference to the pH. The highest pH attained in an uncontaminated sample after the stomach had emptied itself of food was recorded. 2 patients failed to empty their stomachs of food before they awoke in the morning; the samples from both were excluded. Sampling was repeated on a second night in 5 cases; in

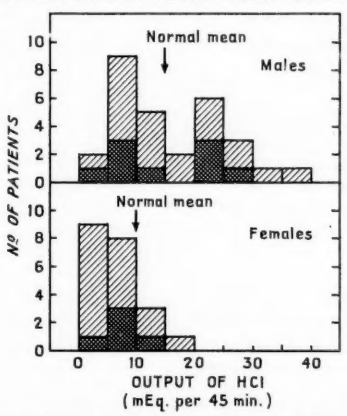

Fig. 2—Distribution of patients according to the quantity of hydrochloric acid secreted in response to histamine.

Cross-hatched areas represent patients who also had a duodenal ulcer. Arrows indicate average amounts secreted by patients without known disease of the stomach (from the data of Kay 1953, Murray et al. 1957, and Marks and Shay 1959).

TABLE I—MEAN QUANTITY OF HYDROCHLORIC ACID SECRETED IN RESPONSE TO HISTAMINE BY 50 PATIENTS WITH GASTRIC ULCER, CLASSIFIED BY SEX, SITE OF ULCER, AND PRESENCE OR ABSENCE OF A DUODENAL ULCER: 3 WOMEN HAD MULTIPLE GASTRIC ULCERS; IN EACH CASE THERE WAS A CRATER IN THE BODY OF THE STOMACH, AND THEY HAVE BEEN CLASSIFIED UNDER THIS HEADING.

Site	Males		Females	
	No. of patients	Mean output of HCl and standard error of mean	No. of patients	Mean output of HCl and standard error of mean
Antrum ..	4	26·6 (±5·4)	1	14·2
Incisura ..	13	17·5 (±1·5)	4	8·9 (±3·4)
Body	12	10·1 (±2·6)	16	5·7 (±1·3)
All sites without D.U.	19	14·9 (±2·1)	16	6·3 (±1·3)
All sites with D.U.	10	17·1 (±3·2)	5	8·0 (±1·7)

each the highest pH differed by less than 1 unit on the two nights.

The histamine test was that of Kay (1953), except that the gastric secretion was collected for one period of forty-five minutes from the time that histamine was given. The volume of the secretion aspirated was recorded, and its acidity determined by titration with phenolphthalein. In the 5 patients in whom the test was repeated the volume differed by less than 25 ml. and the acidity by less than 5 mEq. per litre on the two occasions.

Results

Histamine Test

Fig. 1 is a plot of the volume and acidity of the secretion aspirated after histamine.

The output of hydrochloric acid, taken as the product of the volume and acidity, is shown in fig. 2. The mean output of the 29 men was 15·1 (±2·1) mEq., and of the 21 women was 6·7 (±1·0) mEq. The variation about the mean was greater in men than in women (S.D. 11·3 and 4·6 mEq. respectively). There was no obvious correlation for either sex between the quantity of hydrochloric acid secreted and the patient's age or the length of the history.

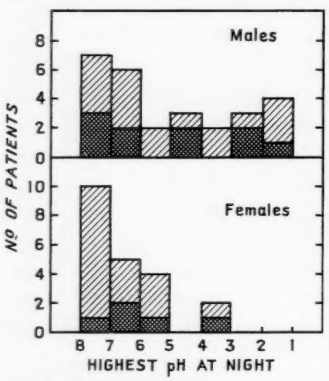

Fig. 3.—Distribution of patients according to the pH of the least acid nocturnal sample.

Cross-hatched areas represent patients who also had a duodenal ulcer.

The distribution of ulcers between the different sites and the mean output of acid for each site are shown in table I. In both sexes the mean output of hydrochloric acid was highest when the ulcer was in the antrum and lowest when it was in the body of the stomach. Relatively more men than women had ulcers of the antrum or incisura. Patients who also had a duodenal ulcer secreted about the same quantity as those who had not. Women with ulcers of the body of the stomach were an exception. The 5 such patients with a duodenal ulcer had a mean output of 8·0 (±1·7) mEq. and the 11 without a mean output of 4·6 (±3·2) mEq.

Nocturnal Sampling

In all the patients the gastric contents were acid so long as food was present. In a majority acidity fell after food had left their stomachs, and reached its lowest level in the early hours of the morning.

Fig. 3 shows the pH of the least acid sample from each patient. Samples became neutral or alkaline more often in women than in men. Patients who had a duodenal ulcer showed a similar distribution to those who had not.

Table II shows that the minimum acidity during the night was related to the site of the ulcer. Neutrality (defined as the presence of at least one sample with a pH greater than 6) was commonest when the ulcer was in the body of the stomach. In all 4 patients with antral ulcers the gastric contents remained acid.

The pH of the least acid sample was compared with the acidity of the histamine secretion (fig. 4).

Discussion

More than one hypothesis has been proposed to account for differences in the concentration of acid in gastric juice. The present findings will be interpreted in terms of the two-component theory, which supposes that the parietal cells secrete hydrochloric acid at a fixed concentration (the acid component) and that this acid is diluted and partly or wholly neutralised by the mixed secretions of other gastric cells (the alkaline component). The data shown in table I are thus misleading to the extent that they fail to take account of partial neutralisation of acid component after its secretion.

TABLE II—NOCTURNAL NEUTRALITY OF THE GASTRIC CONTENTS (DEFINED AS THE PRESENCE OF AT LEAST ONE SAMPLE WITH A pH HIGHER THAN 6) ACCORDING TO THE SITE OF THE GASTRIC ULCER: THE NUMBER OF PATIENTS WHO ALSO HAD A DUODENAL ULCER IS SHOWN IN PARENTHESES.

Site	Neutral	Acid
Antrum (4 patients)	0	4 (*1*)
Incisura (16 patients)	8 (*2*)	8 (*2*)
Body (28 patients)	20 (*6*)	8 (*4*)

Kay (1953) and Marks (1956) have produced evidence that the output of hydrochloric acid in response to a large dose of histamine is, when not modified by drugs or by vagotomy, proportional to the number of parietal cells in the stomach. In both the men and the women the output of hydrochloric acid tended to be abnormally high when the ulcer was in the antrum and abnormally low when it was in the body of the stomach. The relative frequency with which the men had incisural and antral ulcers and the women ulcers in the body of the stomach accords with previous reports (Crisp 1843, Lehmann 1936).

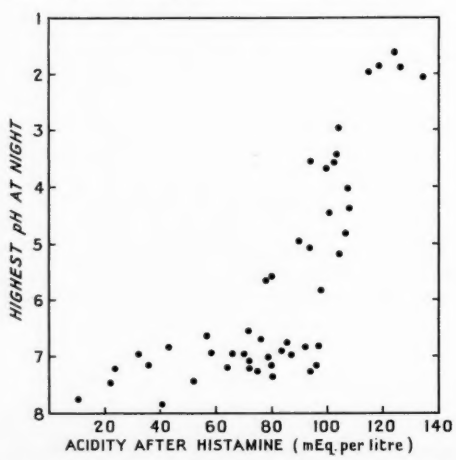

Fig. 4—Relation between the pH of the least acid nocturnal sample and the acidity of the gastric juice after histamine.

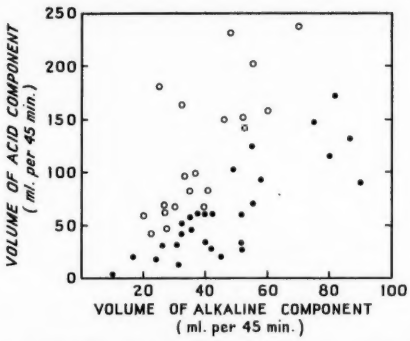

Fig. 5—Volumes of the acid and alkaline components of gastric juice secreted after histamine, calculated from the volume and acidity of the mixed secretion by the formula of Thompson and Vane (1953).
Patients whose nocturnal samples became neutral are shown as black circles, and those in whom they all remained acid as open circles.

If the patients had differed among themselves only in the volume of acid component which they secreted in response to histamine, but all secreted the same volume of alkaline component, the acidity of the gastric juice collected would have varied directly with its volume, the relationship having the form of a hyperbola (Gray and Bucher 1941). The wide scatter shown in fig. 1 indicates that the patients differed in their output of alkaline component independently of the greater differences in their output of acid component—in other words the acidity measured after histamine was not closely related to the quantity of acid component secreted.

Fig. 4 shows that the lowest acidity at night was related to the acidity after histamine; any patient who failed to maintain acid gastric contents at night could attain only a low acidity after histamine. In fig. 5 each patient's histamine secretion is shown in terms of the calculated volumes of the acid and alkaline components which the gastric juice contained (Thompson and Vane 1953); neutralisation took place at night whenever the output of acid was low in relation to that of alkaline component. The rates at which both acid and alkaline components were secreted during the night were functions of the rates at which they were secreted after histamine; but, while the rate of secretion of acid component fell greatly at night, that of alkaline component fell proportionally less, if it fell at all. If this interpretation of the findings is correct, nocturnal neutrality of the gastric contents was caused sometimes by a high rate of secretion of alkaline component, and sometimes by a low rate of secretion of acid.

With the possible exception of women with ulcers of the body of the stomach, patients who had, or had once had, a duodenal ulcer did not differ in their response to histamine or in their gastric acidity at night from patients who had not. These findings contradict the opinion of Marks and Shay (1959) and of Grossman (1960) that patients who have both duodenal and gastric ulcer secrete the same large quantities of acid as patients with duodenal ulcer alone.

Summary

In 50 patients with gastric ulcer the responses to a large dose of histamine were studied and the gastric contents were sampled during the night.

Patients with antral ulcers tended to secrete a large quantity of acid in response to histamine; those with ulcers in the body of the stomach tended to secrete a small quantity. The concentration of acid attained in the gastric juice after administration of histamine was not closely related to the quantity of hydrochloric acid secreted.

The nocturnal samples became neutral in a majority of patients with ulcers in the body of the stomach, but not at all in patients with antral ulcers. Patients whose nocturnal samples became neutral secreted acid at a lower concentration in response to histamine than those in whom the samples were all acid.

It is suggested that nocturnal neutralisation was in some cases the result of an excessive secretion of an alkaline component of gastric juice, while in others it was due to a diminished secretion of the acid component.

There were only minor differences in secretory behaviour between patients who also had duodenal ulcers and those who had not.

I am indebted to those physicians and surgeons who have allowed me to study their patients, and to Prof. Harold Scarborough and Dr. A. H. James for helpful criticism. The work was done during tenure of the Cardiff Royal Infirmary research fellowship in medicine.

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THE HISTOLOGICAL BACKGROUND TO GASTRIC ULCER

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GASTRIC ulcers are surrounded by a zone of inflammation of variable width, but even beyond this zone the remainder of the gastric mucosa is not usually normal. Diffuse abnormality of the gastric mucosa, involving both the epithelium and the glandular layer, has been described by Konjetzny (1930) and by Magnus (1937, 1946), and is often called gastritis, because there is conspicuous round-cell infiltration of the lamina propria. The epithelial changes are of two kinds: either a reduction in height and a change in the staining properties of the epithelial cells, or metaplasia into cells of intestinal type. The glandular changes are a variable reduction in the number of zymogenic and acid-forming glands, and partial replacement of these glands by clear-celled glands similar to those usually seen in the pyloric antrum.

Two-thirds of patients with gastric ulcer are abnormal in that their gastric contents are anacid after food has left the stomach at night; the remaining third behave normally in having weakly acid gastric contents at this time (James and Pickering 1949, Watkinson 1951, Chandler and Watkinson 1959). Ball (1961) showed that this abnormality could be ascribed sometimes to a diminished power to secrete acid and sometimes to an excessive secretion of the alkaline component of gastric juice.

We report here a comparison of the histological

appearances of the gastric mucosa of resected stomachs with the secretory behaviour determined before operation.

Patients

The patients were the 25 from the series of Ball (1961) submitted to partial gastrectomy. There were 17 men and 8 women. 5 of the men and 2 of the women also had duodenal ulcers. The operations were performed electively for conventional reasons. Our series includes only 2 patients who secreted less than 5 mEq. of hydrochloric acid in response to histamine.

Methods

Nocturnal samples were obtained and histamine tests done as described by Ball (1961). Not more than two weeks elapsed between the secretory tests and operation.

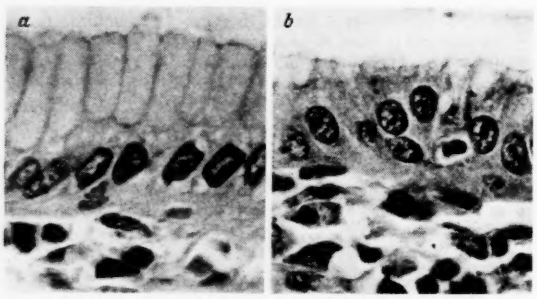

Fig. 1—(*a*) Normal and (*b*) abnormal epithelium in sections from the body of the stomachs of two patients of this series. (×1500.)

Immediately after operation the resected portion of stomach was placed in formol-saline. Strips of mucosa about $1^1/_2$ in. (3·75 cm.) long were taken from two sites, each at least 2 in. (5 cm.) from any ulcer crater—one from the greater curve at the proximal end of the specimen; and one from the antrum, if possible on the lesser curve. Sections were stained with hæmatoxylin and eosin.

We each assessed independently the appearances in sections from all the cases when the series had been completed. Neither observer knew from which patient, or from which part of the stomach, each slide came. We assessed the following features:

1. *Epithelium.*—This was classified, separately on the free surface and in the gastric pits, as normal or abnormal. Abnormality meant not intestinal metaplasia (which was noted separately) but a reduction in the height of the cells and a lack of the large intracellular mucous droplets which, in contiguity, give healthy gastric epithelium its distinctive histological appearance (fig. 1). Although grades of abnormality were seen it was not possible to express these quantitatively. Sometimes the abnormality was patchy, in which case the section was classed as abnormal.

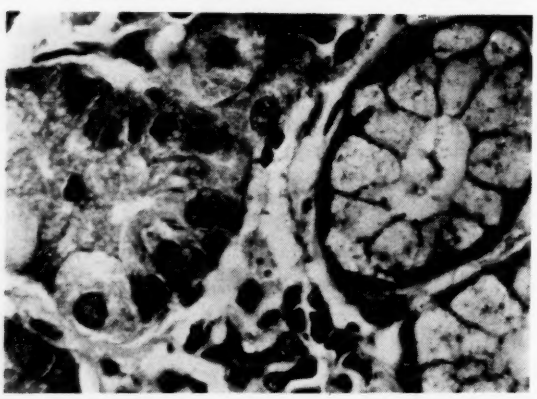

Fig. 2—Section from the body of stomach, showing replacement of fundic by antral glands, with parietal and zymogenic cells on left and antral tubules on right. (×1500.)

TABLE I—NUMBER OF PATIENTS WITH NORMAL OR ABNORMAL GASTRIC EPITHELIUM, CLASSIFIED ACCORDING TO GASTRIC ACIDITY AT NIGHT

Site of section	Neutral (15 patients)			Acid (10 patients)		
	Normal	Observers disagree	Abnormal	Normal	Observers disagree	Abnormal
Body:						
Surface	0	1	14	5	1	4
Pits ..	1	5	9	8	1	1
Antrum:						
Surface	1	0	14	5	1	4
Pits ..	1	0	14	6	0	4

2. *Antral glands.*—Antral glands might occur among fundic glands (fig. 2), or they might form the only visible glandular tissue. Their presence or absence was recorded.

3. *Intestinal metaplasia.*—This was noted as present or absent in each section. Epithelium between patches of intestinal metaplasia might be normal or abnormal in the sense defined above.

The data from secretory and histological studies, as well as age, sex, site of ulcer, duration of symptoms, and presence or absence of duodenal ulcer were recorded on punched cards, and possible correlations sought taking each item in turn as an independent variable.

Results

Two sets of strong correlations emerged. Patients with nocturnal neutrality, as defined by Ball (1961), and patients whose ulcer was in the body of the stomach tended to show histological abnormality very often. Those with acid nocturnal contents, and with antral ulcers, much more often had normal gastric mucosa. Cases of " incisural " ulcer lay intermediately. Site of ulcer and the occurrence of nocturnal neutrality are themselves associated, as has already been demonstrated (Watkinson 1951, Ball 1961).

TABLE II—NUMBER OF PATIENTS WITH NORMAL OR ABNORMAL EPITHELIUM, CLASSIFIED ACCORDING TO SITE OF GASTRIC ULCER

Site of section	Body (13 patients)			Incisura (9 patients)			Antrum (3 patients)		
	Normal	Observers disagree	Abnormal	Normal	Observers disagree	Abnormal	Normal	Observers disagree	Abnormal
Body:									
Surface ..	1	0	12	1	2	6	3	0	0
Pits	1	4	8	5	2	2	3	0	0
Antrum:									
Surface ..	1	1	11	3	0	6	2	0	1
Pits	2	0	11	3	0	6	2	0	1

Tables I–IV show the degree of association. Table II, relating to epithelial abnormality, shows that the gastric pits were less severely affected than the surface.

Tables III and IV show that replacement of fundic by antral glands was associated with a secretory behaviour and with site of ulcer in the same way as epithelial change; but the glandular changes were less often present, and when present were less prominent than the epithelial.

Tables V and VI show, by contrast, that intestinal metaplasia was not associated with secretory behaviour or site of ulcer.

Classification by age, sex, length of history, or the presence of a duodenal ulcer gave no significant correlations. When we expressed the results of the histamine tests in terms of output of acid and alkaline components

TABLE III—NUMBER OF PATIENTS WITH ANTRAL GLANDS IN SECTIONS FROM BODY OF STOMACH, CLASSIFIED ACCORDING TO GASTRIC ACIDITY AT NIGHT

Neutral (15 patients)			Acid (10 patients)		
Absent	Observers disagree	Present	Absent	Observers disagree	Present
3	3	9	7	2	1

TABLE IV—NUMBER OF PATIENTS WITH ANTRAL GLANDS IN SECTIONS FROM BODY OF STOMACH, CLASSIFIED ACCORDING TO SITE OF GASTRIC ULCER

Body (13 patients)			Incisura (9 patients)			Antrum (3 patients)		
Absent	Observers disagree	Present	Absent	Observers disagree	Present	Absent	Observers disagree	Present
2	3	8	6	1	2	2	1	0

(Thompson and Vane 1953) there was some association of output of alkaline component with the state of the epithelium, but the correlation was less close than those shown in tables I–IV.

Discussion

No study of the associations between characteristics can itself establish cause and effect. Although these associations could be explained in several ways, two seem to us to be most likely:

1. A secretory disturbance, one of two possible kinds, leads to nocturnal neutralisation which in turn damages the superficial epithelium and predisposes to ulceration. This secretory disturbance may sometimes be reflected in glandular metaplasia in fundic sections.

2. Both nocturnal neutralisation and damage to the mucosa are the results of ulceration (Watkinson 1951, Marks and Shay 1959).

We prefer the first hypothesis; if the ulcer were the cause of the secretory changes it would be necessary to suppose that ulcers could sometimes augment secretion of the alkaline component and sometimes diminish acid secretion. It also seems more likely that an epithelial change as widespread as this one results from an alteration in the gastric contents, which bathe the whole stomach lining, rather than from a local lesion. The inflammatory zone around an ulcer does not spread far from the ulcer itself.

TABLE V—NUMBER OF PATIENTS WITH INTESTINAL METAPLASIA OF GASTRIC EPITHELIUM, CLASSIFIED ACCORDING TO GASTRIC ACIDITY AT NIGHT

Site of section	Neutral (15 patients)			Acid (10 patients)		
	Absent	Observers disagree	Present	Absent	Observers disagree	Present
Body ..	12	2	1	10	0	0
Antrum ..	3	3	9	4	0	6

We therefore suggest that periods of abnormal alkalinity of the gastric contents can leave the epithelium liable to damage of the kind illustrated in fig. 1b. The continuous layer of intracellular droplets shown in fig. 1a is composed of mucus (Bensley 1932, Schindler 1944). Gastric mucus is profoundly affected by hydrogen-ion concentration; acid precipitates it, and application to the human stomach of hydrochloric acid even at a concentration of 1000 mEq. per litre was found by Wolf and Wolff (1948) to have no other effect than to stimulate the formation of a coating of precipitated mucus. As acidity falls, however, mucus becomes a gel, and at neutral reactions it is fluid. We suppose that, so long as the gastric contents are acid, the intracellular mucus of the epithelial cells is prevented from escaping by a precipitated layer of mucus on the surface. During periods of neutrality, however, the surface mucus becomes fluid, permitting loss of mucus from the cells. In this way the mucous barrier may be weakened or removed.

TABLE VI—NUMBER OF PATIENTS WITH INTESTINAL METAPLASIA OF GASTRIC EPITHELIUM, CLASSIFIED ACCORDING TO SITE OF GASTRIC ULCER

Site of section	Body (13 patients)			Incisura (9 patients)			Antrum (3 patients)		
	Absent	Observers disagree	Present	Absent	Observers disagree	Present	Absent	Observers disagree	Present
Body	10	2	1	9	0	0	3	0	0
Antrum	2	3	8	3	0	6	2	0	1

Summary

Nocturnal gastric sampling and histamine tests were carried out in 25 patients with gastric ulcer who subsequently had gastrectomies.

Sections of mucosa from the body of the stomach and from the pyloric antrum, but remote from the ulcer, were assessed by observers ignorant of the source of the individual sections.

Loss of intracellular mucus from the surface epithelium was commonly observed. This change was mainly found in cases where the gastric contents were neutral at night and the ulcers were in the body of the stomach. Patients with antral ulcers tended to have acid gastric contents at night and normal gastric epithelium.

The epithelial changes were, it is suggested, caused by noctural neutralisation.

We are indebted to our colleagues who allowed us to study their patients; to the staff of the pathology department who prepared the sections; to Mr. R. Marshall for the photomicrographs; and to Prof. Harold Scarborough for helpful criticism. One of us (P. A. J. B.) held the Cardiff Royal Infirmary research fellowship in medicine while this work was being done.

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DIMETHYLDIGUANIDE IN THE TREATMENT OF DIABETIC CHILDREN

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IN the treatment of diabetic children the replacement of insulin injections by an orally effective drug is desirable, but carbutamide (Chute and Bain 1956, Barta 1957, Camerini-Davalos et al. 1957, Smellie 1958) and tolbutamide (Camerini-Davalos et al. 1957) are ineffective. Early reports suggested that the diguanides—particularly phenethylformamidinyliminourea (D.B.I.) and normalamylformamidinyliminourea (D.B.B.)—might be more effective than are the sulphonylureas in acute juvenile diabetes, but

the gastrointestinal disturbance which occurs in almost half the patients treated (Krall et al. 1958) interferes with their use in children. More recently effectiveness and better gastrointestinal tolerance have been claimed for dimethyldiguanide metformin (Azerad and Lubetski 1959), although in a British trial by Granville-Grossman et al. (1959) the compound, while proving more effective than the sulpho-nylureas, gave rise to so much nausea, vomiting, or diarrhœa in adults that it seemed to offer no particular advantage. Unpublished French reports suggest that dimethyldiguanide (referred to hereafter as D.M.G.) is effective in children not only in reducing the blood-sugar but also in stabilising the "brittle" case and in decreasing the frequency of insulin reactions where insulin is still being used. All of these are good reasons for testing D.M.G. in diabetic children, and a pilot study has been carried out.

Method

The aims of the trial were firstly to show whether D.M.G. would reduce the glycosuria and/or insulin requirement in diabetic children, and secondly to evaluate possible toxic and side effects. For these purposes a "double blind" technique commended itself. Because of the common partial and the rare complete temporary remissions in the early months after the start of insulin treatment of the child, all those chosen for study had had the disease for at least 18 months. There were five boys whose ages were $5^1/_2$, 6, $7^1/_2$, 11, and $11^1/_2$ years, and five girls aged 9, 10, $11^1/_2$, 12, and 14. In hospital the life of the child is so restricted that consistent control of diabetes may be surprisingly difficult. For this reason the children were allowed to remain at home. Reliable results of preprandial urine-sugar tests ('Clinitest') done four times daily * were available for each child during a 1-year period before the trial, and each patient's therapeutic and daily routine remained quite unchanged except for the addition of D.M.G. or the placebo. Tablets of D.M.G. have a repulsive taste, so capsules containing 250 mg. and dummy capsules containing 250 mg. of calcium phosphate (*B.P.*) flavoured with a trace of dimethyl phthallate were prepared. These looked identical, and the children experienced no difficulty in swallowing them. The whole supply was kept by the hospital pharmacist who, unknown to those conducting the trial, designated the dummy ones "A" and those containing dimethyldiguanide "B".

* These were preferred to the measurement of 24-hour urinary sugar output as the collections impose unnatural restriction of activity.

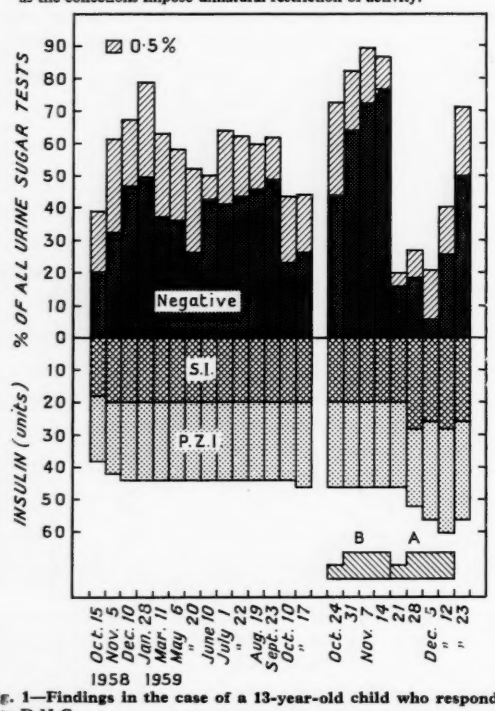

Fig. 1—Findings in the case of a 13-year-old child who responded to D.M.G.

Glycosuria was reduced while administration of the drug was continued. Rebound glycosuria followed its withdrawal.

The urine sugar results are derived from the total number of tests carried out between successive attendances at the clinic.

S.I.—soluble insulin. P.Z.I.—protamine zinc insulin.

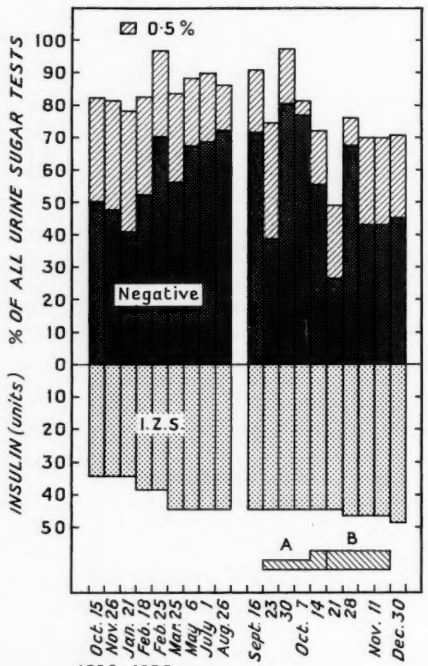

Fig. 2—Findings in the case of a 12-year-old child who showed no significant response to D.M.G.

I.Z.S.—insulin zinc suspension.

For each child the duration of the trial was 8 weeks. The children started by taking one capsule of either "A" or "B" thrice daily with meals for 1 week, and then took two thrice daily for the next 3 weeks. They then changed to the other capsule thrice daily, and the schedule was repeated. Through an oversight three of the children received the double dose of "B" for only 1 week. At the start of the trial, after 4 weeks, and at the end samples of venous blood were taken from each patient for elementary tests of renal and hepatic function. Weekly attendances were made at the diabetic clinic throughout the trial period, and the quality of diabetic control was assessed by the usual criteria. Weight and height were recorded, and the capillary blood-sugar was measured. Special attention was paid to the degree of glycosuria, and a record was made of the percentages of urine tests which were (*a*) negative for sugar, and (*b*) ranged between negative and 0·5% during each weekly period. Inquiries were made for hypoglycæmic episodes, gastrointestinal disturbances, appetite, and wellbeing. Alterations in insulin dosage were made only if clearly indicated.

Results

During the trial it was noted that six of the ten children taking capsule "B" showed significant reduction in glycosuria with or without certain side-effects, and at the end it was disclosed that these capsules contained the D.M.G. One child showed a comparable reduction while on the placebo. The results obtained in one of the

children who responded to D.M.G. are shown in fig. 1, while fig. 2 illustrates a case in which no significant change occurred.

Four of the children developed distinct side-effects when the dose of D.M.G. was raised to the maximum level of 500 mg. t.i.d. These consisted of anorexia, nausea, abdominal discomfort (described variously as "funny tummy", "hot tummy", &c.), and diarrhœa. In addition, these four children showed characteristic changes in their behaviour, consisting in a loss of *joie de vivre*, a rather uninterested, lack-lustre appearance, and at the worst an unfavourable view of life in general. In three of these children it was impossible to persist with the maximum dose for more than a day or two at a time, although one child seemed eventually to adapt himself and during the fourth week was largely free of such symptoms. One girl complained when on D.M.G. that "everything tastes funny"—milk, for example, always seeming sour. Presumably some of the symptoms were hypoglycæmic in origin, but it was noteworthy that the children never felt hungry. In all but one child the single blood-sugar determinations taken at least 2 hours after a meal at each clinic attendance showed no significant decrease during D.M.G. administration. It was our impression that even on the smaller dose of D.M.G. most of the children had slightly diminished appetites. A reduction in insulin (by 13, 27, 42, 27, and 22%) was found necessary in five of the children during D.M.G. administration, and with one exception these were the patients that had the most severe side-effects. None of the children showed disturbance of hepatic or renal function.

The most consistent single feature of the trial was a "rebound" increase in glycosuria immediately after withdrawal of D.M.G. In eight of the ten children participating in the trial the withdrawal of D.M.G. was immediately followed by a striking increase in glycosuria to levels much in excess of those found during the control period. The rebound glycosuria was at its height during the first week after withdrawal of D.M.G. (fig. 1) and did not persist longer than 2 or 3 weeks. There was no accompanying ketonuria or clinical disturbance.

Conclusions

In this double-blind trial dimethyldiguanide metformin reduced glycosuria in most of the diabetic children treated, and on its withdrawal their glycosuria became temporarily more severe.

Insulin remained necessary in all, and, although reductions of up to 42% were achieved, these reductions were not offset by enhanced stability of control, and indeed use of the drug was associated with disadvantageous side-effects in most of the children.

Under the rigid conditions of this limited trial the drug offered no advantage to the diabetic child. On the contrary it complicated control by adding yet a further variable to such others as diet, insulin, exercise, mood, and co-operation by parent or child.

We are indebted to Rona Laboratories Ltd. for generous supplies of 'Glucophage' (D.M.G.) and control capsules, and to Mrs. E. Armour, pharmacist of the Royal Hospital for Sick Children, for having arranged the issue of test and placebo capsules.

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XX/XO MOSAICS IN TURNER'S SYNDROME

Two Further Cases

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FEW cases of mosaicism have been reported in Turner's syndrome. In 1957, Danon and Sachs suggested, on the basis of sex-chromatin studies, that two of their patients might be XX/XO mosaics. Later, Ford et al. (1960) concluded from chromosome studies that one and probably two patients of theirs were XX/XO mosaics. Sandberg et al. (1960) reported of two further cases, and Fraccaro et al., Blank et al. (1961), and Ferrier et al. (1961) have each described one example. We here report two further cases.

Case-reports

THE FIRST CASE

The patient, aged 15, of female phenotype, came under observation because of retardation of growth and puberty. Her father, of Italian descent, measures 5 ft. 8 in. (1·72 m.). Her mother, who was born in Morocco, measures 5 ft. 2 in. (1·58 m.), and menstruated at the age of 14. The patient is the third child of a sibship of six otherwise normal children. She measures 4 ft. 6 in. (1·37 m.) and weighs 68 lb. (31 kg.), average figures for her age being 5 ft. 1 in. (1·56 m.) and 99 lb. (45 kg.). Her appearance is still infantile, with hardly any breast development, very scanty pubic hair, and no axillary hair. She has never menstruated. There is no webbing of the neck. X-ray examination revealed a normal bone age and no skeletal malformation.

A gynæcologist reported that the vagina was of normal length, but at rectal examination the uterus was found to be very small and the gonads were not palpable. A vaginal smear favoured the diagnosis of ovarian insufficiency (20% basal cells, 60% intermediary cells, and 20% superficial cells). The figures for hormone excretion varied, as follows: follicle-stimulating hormone between 3 and 25 units per 24 hours; 17-ketosteroids 1·10–3·25 mg. per litre; 17–21-hydroxysteroids 3·40–5·0 mg. per litre; Porter and Silber's test 5·10–6·5 mg. per 24 hours; the blood-count, and blood sugar, total cholesterol, calcium, and phosphorus, are within normal limits.

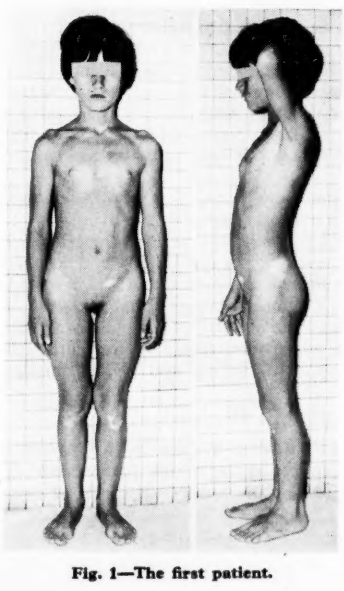

Fig. 1—The first patient.

The patient's intelligence is rather low as shown by different standard tests (I.Q. 101). Moreover she has several pigmented nævi surrounded by a non-pigmentary area of skin, which are characteristic of Sutton's disease.

THE SECOND CASE

This patient, now aged 16½ years, came to our notice at the age of 14 also because of retardation of growth and puberty. Her mother, aged 45, and her father, aged 55, are small, measuring 5 ft. and 5 ft. 1 in. (1·54 and 1·55 m.) respectively. She is the fourth child of a sibship of eight. At the age of 14, she measured 4 ft. 5 in. (1·32 m.)—pubis-ground 23 in. (59 cm.) and crown-pubis 29 in. (73 cm.)—and weighed 85 lb. (39 kg.). X-ray examination revealed a bone age of 12 years. Now she measures 4 ft. 7 in. (1·39 m.) and weighs 96 lb. (44 kg.). Her appearance is feminine, although she is rather stocky, with a broad chest and bilateral mild cubitus valgus. There is no neck webbing.

The external genitalia are female but infantile. Scanty pubic hair appeared at the age of 14 and has hardly grown since.

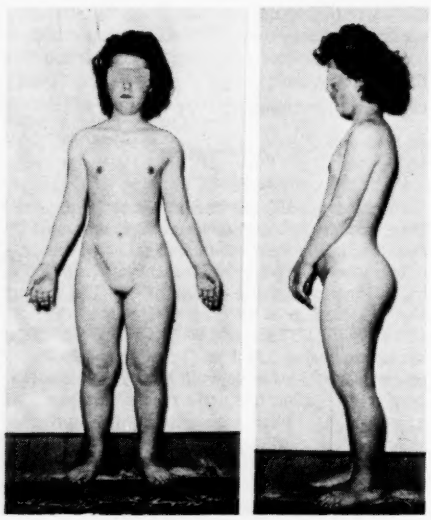

Fig. 2—The second patient.

Axillary hair is absent. The breasts are very small. The vagina and the uterus are about the size usual in a girl of 8.

Hormone-excretion studies at the age of 14 showed that the follicle-stimulating hormone was more than 96 units per 24 hours, and the ketosteroids were about 1 mg. per 24 hours. Menses have since been induced artificially, but the results have been irregular. Other tests, including blood-count, and blood sugar, total cholesterol, calcium, and phosphorus are within normal limits.

The patient is of normal intelligence (I.Q. 110). She was a good pupil at school, and now earns a reasonable living.

Recently, because of appendicitis, laparotomy was performed through a large incision, revealing the small uterus and normal-looking ligaments. No gonads could be found either in the normal sites or in the inguinal region. Examination of a biopsy specimen confirmed the absence of gonadal tissue and showed that the uterine tubes were underdeveloped although they had well-defined epithelial fringes and plexus muscle-fibres.

NUCLEAR SEX AND CHROMOSOME ANALYSIS

In both cases buccal mucosal smears were consistent with a female genotype, although the proportion of chromatin-positive cells was low—16% in the first case and 18% in the second.

The chromosomes were studied by culturing a fragment of aponeurosis (fascia lata in the first case and abdominal aponeurosis in the second) as described by Lejeune et al. (1960). Chromosome-counts (shown in the table) gave two modes, one at 45 and one at 46. Analysis of cells with 46 chromosomes revealed a normal female karyotype, but the cells with 45 chromosomes showed a consistent pattern of Turner's syndrome—i.e., 45/XO chromosomes. On the basis of this and the nuclear sex, we concluded that both patients were XX/XO mosaics.

CHROMOSOME-COUNTS

Case no.	Total no. of cells	Cells with 45 chromosomes	Cells with 46 chromosomes
1	27	15	12
2	22	12	10

Discussion

The patients are much alike. They have the major symptoms of Turner's syndrome—namely, growth retardation, amenorrhœa, and failure of puberty—without other important symptoms such as webbing of the neck and skeletal malformations, except for mild cubitus valgus in the second case.

If it had not been for the chromosomal findings the first case would have been dismissed with the diagnosis of delayed puberty, especially as many members of the patient's family are small. The second patient also belongs to a stock of small size, but here laparotomy and histology showed the gonadal agenesis (which is likely, too, in the first case). On the other hand, the fact that the nuclear sex was chromatin-positive does not orient the diagnosis towards Turner's syndrome except for the rather low proportion of chromatin-positive cells. Incidentally, this proportion is in agreement with the fact that only a fraction of the patient's cells are XX.

People with an XX/XO mosaic seem to show a mild, or rather truncated, Turner's syndrome, comprising gonadal agenesis, failure to menstruate and to initiate puberty, underdeveloped genitalia, scanty pubic hair, no axillary hair, underdeveloped breasts, and nearly normal hormone production, but without the usual malformations of the complete Turner's syndrome. Unfortunately the clinical details have not yet been published of the cases described by Ford (1960) and Sandberg et al. (1960). Hence we cannot yet discuss the general application of our conclusions.

The problem of the origin of XX/XO mosaicism is only part of that pertinent to all mosaics. The view most favoured is that, early in the embryo's development, because of non-disjunction, a clone of cells arises with a chromosome set different from that of the zygote. In the case of XX/XO mosaics, Ford et al. (1960) favour the possibility of an XX clone arising in an XO embryo, rather than the opposite, because an XX cell would be at advantage in an XO embryo, whereas an XO cell would be at disadvantage in an XX embryo.

Summary

Two cases of XX/XO mosaicism are reported. They were very similar, having major symptoms of Turner's syndrome—i.e., physical underdevelopment, failure to menstruate, infantile genitalia, little pubic hair, underdeveloped breasts, and gonadal agenesis—without the usual malformations except for mild cubitus valgus in one case. Their nuclear sex is of the female type, but with a low proportion (16–18%) of chromatin-positive cells.

Chromosome-counts showed about half XO cells and half XX cells.

We should like to acknowledge the financial support of the Institut National d'Hygiène, Paris (Prof. L. Bugnard), and the U.S.A. National Institute of Health (grant no. M.3921); and the technical assistance of Miss M. Roubin.

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PSYCHIATRIC SEQUELÆ OF CHRONIC EXPOSURE TO ORGANOPHOSPHORUS INSECTICIDES

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THE phosphate-ester insecticides were first introduced about fifteen years ago, and since then a large number have been developed. In man, toxic effects and death have been reported after acute exposure to these compounds (Bidstrup et al. 1953, Koelle and Gillman 1946, 1949, Hunt and Riker 1947, Grob et al. 1947, 1949, 1950, Abrams et al. 1950), which are all potent inhibitors of the cholinesterases. Acute poisoning resembles that produced by excessive stimulation of the parasympathetic nervous system; and this group of compounds may, therefore, be classed as parasympathomimetic stimulants or cholinergic agents. Acute toxic episodes are not infrequent; and severe systemic disturbances caused by their muscarine-like and nicotine-like actions have been widely reported. But no accounts have been published of the psychiatric sequelæ of chronic exposure, with or without acute episodes of intoxication. It is of considerable academic and practical interest to see whether there is any seasonal or geographical variation in the incidence of these conditions in districts where these insecticides are used, and to determine the role of cholinesterase and the levels of acetylcholine in mental disease.

Case-reports

So far we have seen 16 cases; in 7 the diagnosis was made by independent psychiatrists. 3 were scientific officers studying the efficacy of the sprays; 8 worked in greenhouses; and 5 were farmworkers. Two types of reaction were seen—schizophrenic and depressive.

CASE 9

A 26-year-old scientific field officer, with no previous history of mental illness and no relevant family history, who had been healthy and taken part in sporting and social activities at the university, had been employed since 1956 in checking the efficacy of organophosphorus insecticides. To do this he had to handle leaves and branches; and he was exposed to parathion and malathion during the first two years, and 'Trithion' (O, O-diethyl S-*p*-chlorophenylthiomethyl phosphorodithioate) and azinphos-methyl ('Gusathion'; O, O-dimethyl-S[4-oxobenzotriazino-3-methyl] phosphorodithioate) in the third and fourth. He wore standard clothes, but no protective garments or gloves.

He showed mild symptoms of poisoning intermittently over the four years. At the end of 1957 he complained of nausea, vomiting, and pains in the chest; and indigestion was diagnosed. In 1959 he had cramps in the arms and legs, dizziness associated with mild pyrexia, and some generalised muscle fasciculation. Difficulty in focusing was noted occasionally. He was constantly tired although he slept for longer than before; and he took sickleave more and more often.

From December, 1959, to February, 1960, he studied the effects of trithion and azinphos-methyl. He experienced severe cramps and giddiness on two occasions; and the second time he also had a severe migraine-like headache, and muscle fasciculation, and was admitted to hospital. He was very restless, irritable, tense, and anxious, had severe insomnia, and was considered to be in an anxiety state. Two weeks after admission the blood-cholinesterase level estimated by the method of Fleischer et al. (1956) was found to be 50% of the theoretical normal. He was given an injection of 1 g. pyridine-2-aldoxime methiodide (2-PAM) which for a time relieved his peripheral symptoms considerably. He was admitted again in March, given atropine and 2-PAM, and discharged improved.

Early in May, 1960, he was admitted to hospital with an acute psychosis; a diagnosis of schizo-affective disorder was made. He was garrulous and restless, and had schizophrenic ideas of religious influence, of being close to God, of being called to Rome to replace the Pope, and other related bizarre ideas; and he was actively hallucinated. Chlorpromazine and a course of 21 sessions of electroconvulsive therapy (E.C.T.) were given, and he was discharged in July.

When seen again in September, 1960, he was still unable to work. His parents said that even before the E.C.T. he had had difficulty in concentrating, and in putting his thoughts together; and he now felt constantly tired, was cranky and irritable, could not do things as easily as before, and was "like a zombie". He stayed at home, sitting about the house and the garden and did nothing. This pattern of behaviour was unusual for him.

He himself complained of disturbances of vision, described as difficulty in focusing, associated with a dizzy feeling; he also had difficulty in judging distances and in placing his feet accurately when walking.

He had peculiar feelings of not being fully aware of things around him, though he found it difficult to define this more clearly. The outlines of objects appeared hazy and ill-defined; this also applied to his feelings, and was not purely a visual difficulty.

Fairly gross amnesia was present, for he could not remember about his admissions, what his illness was, or even that he was engaged. He was also spatially disorientated, and had difficulty in finding his way to a well-known nearby suburb by car. Some personality change was evident—e.g., at a railway level-crossing he went through the exit gate rather than the entrance gate and pushed his way through the people coming out, which he himself thought was a funny or stupid thing to do.

He also spoke of sensations of walking on a cloud, and of not really feeling in contact with others. He sometimes found himself doing things he did not intend to, and then wondering why he did them.

He complained of a dull, frontal and occipital headache, and of a feeling of impending disaster, of nervousness, muscle twitches, hand tremor, sensitivity to noise, nausea, anorexia, chest pain, and restlessness. Other people irritated him; and he was still tired, and had some diarrhœa.

Muscle fasciculation, nystagmus, and mild ataxia were still present. He was no longer taking medicine.

He resumed work in November, 1960, and by December was reported to be feeling fit and well, and to be coping very satisfactorily with his job.

CASE 4

A man of 43, a greenhouse technician, had been exposed to insecticides, including parathion and malathion, for ten years, and had complained from time to time of nausea, vomiting, excessive perspiration, giddiness, and muscular incoordination. He had become more and more tired, had difficulty in sleeping, and was very worried by the impairment of his mental ability.

In 1959 he consulted a psychiatrist because of severe depression. He was restless and miserable, had nightmares, and could not sleep. He was irritable, cried occasionally, and felt unable to carry on at work or at home. He was given sedatives at night, and phenelzine (' Nardil ') and other antidepressants; but his condition improved only slightly.

Seen in July, 1960, four months after all exposure had ceased, he complained of headache, digestive troubles, impaired memory, and difficulty in concentration. He could not remember the number and names of the plants under his care; and he found difficulty in understanding anything he read.

In December, 1960, he was almost as well as before exposure. He was no longer depressed and slept properly, and memory and concentration were restored to normal.

CASE 8

A man of 30, employed as a horticultural technical officer, was admitted to a mental hospital in March, 1960. Several weeks before admission, he had been poisoned by an insecticide he was spraying. Classic parasympathomimetic symptoms developed, but he recovered in twenty-four hours. He stated that he had felt for some time that there was a move afoot to force him to transfer to another division. Some were against him and others on his side; but someone intended to shoot him. Even when he was alone, he had heard voices talking about this: the wireless had referred to it; and people in the street stared at him and this had terrified him.

His friends had noticed psychotic behaviour for only a few days before his admission, but he himself said that he had been persecuted for months. Paranoid schizophrenia was diagnosed; he was treated with E.C.T. and discharged apparently well in April, 1960.

CASE 13

A man of 23 had been a farmworker for eight years and exposed to triple-strength malathion and other insecticides for the past four. He never wore any protective clothing.

In 1958, he was twice poisoned and admitted to hospital. Each time he vomited, salivated, sweated profusely, and was weak and confused. He was given atropine. Since 1958 he has not used malathion but ' Sevin ' (1-naphthyl-N-methylcarbamate), another cholinesterase inhibitor.

He was admitted again in 1960. In the past 12 months he had noticed a gradually increasing apathy, difficulty in concentration, excessive sweating, and general retardation. He could not work as before. He had had blurring of vision and palpitations. He was admitted after a fugue when he was found 90 miles from his home and did not know how he had got there. While in hospital he had another fugue, during which he fell and fractured his nasal bones. In hospital he complained of impaired memory and concentration. He walked in his sleep. There were no abnormal physical findings, but the electroencephalogram (E.E.G.) showed abnormal slow activity which reverted to normal just before his discharge four weeks later. His blood-cholinesterase level was 60% of normal.

A neurological lesion had been excluded, but he was discharged with his condition essentially unchanged.

To date 16 cases of chronic exposure have been investigated; the results are given in the accompanying table.

Case no.	Exposure (yr.)	Type of work	Effects on central nervous system
1	9	Technical officer (greenhouse technician)	Depression, headache, impaired memory, fatigue, irritability.
2	9	" "	Depression, memory impaired, gastrointestinal symptoms, irritability.
3	4	" "	Dullness, irritability, depression, concentration and memory impaired.
4	10	" "	Severe depression, nightmares, impairment of concentration and memory, headache, irritability.
5	4	" "	Headache, concentration and memory impaired.
6	2	" "	Headache, fatigue.
7	2	" "	Schizophrenic reaction, paranoidal ideation, ideas of reference, impaired memory and concentration.
8	1½	" "	Schizophrenic reaction: paranoia (2 episodes) and auditory hallucinations.
9	4	Field officer (scientific)	Schizophrenic reaction: auditory religious hallucinations.
10	3	" "	Schizophrenic reaction: apathy.
11	4	Farmer	Schizophrenic acute reaction: agression.
12	5	"	Severe depression.
13	4	"	Fugues, somnambulism, impairment of memory and concentration.
14	3	"	Depression.
15	8	Scientific officer	Depression, impaired memory and concentration.
16	2	Contract sprayer (farmer)	Speech difficulties, waxing and waning of consciousness.

All the cases fell essentially into two main categories—depressive and schizophrenic. Of 16 patients, 7 were depressives and 5 schizophrenics, and in 1 a fugue was the presenting symptom. In the remainder the chief problem was impaired memory and concentration; but in all 16 memory and concentration were sufficiently disturbed to interfere seriously with work and reading ability. 11 had had acute poisoning with the classical signs and symptoms.

Effects on the Central Nervous System

The toxic manifestations are both muscarinic and nicotinic in type. These have been fully reported, but the effects on the central nervous system are not so well known:

- Giddiness, floating sensations
- Tinnitus, nystagmus, pyrexia
- Tremor, ataxia
- Paralyses, paræsthesiæ, polyneuritis
- Speech difficulties:
  - slurring
  - difficulty in forming words
  - changes in speech
  - repetition of syllables
  - difficulty in saying what is intended
- Memory defect—slowness of recall
- Insomnia
- Lassitude and weakness
- Drowsiness
- Concentration difficulty
- Mental confusion
- Uneasiness
- Restlessness
- Anxiety
- Tremulousness
- Emotional lability
- Depression with weeping spells and insomnia
- Schizophrenic reaction
- Dissociation
- Somnambulism and excessive dreaming
- Fugue

Field Survey

It was now important to see if these psychiatric disturbances were commoner where the organophosphorus insecticides were used. Two separate fruit-growing districts were chosen; and 16 local physicians were asked whether they thought mental ill-health had increased and, if so, whether those in the country were more affected than the town dwellers.

Most believed that it had not increased; three, however, thought that depression at any rate was commoner in orchardists, and two supported this by case-records.

Further inquiries were made among orchard supervisors, police, and pharmacists. It was also learnt that in hot weather, safety precautions are almost entirely neglected. It seems to be the general rule that if a worker is acutely poisoned the episode is so distressing that he either takes more precautions or refuses to handle the material at all.

The evidence of an increase in psychiatric disorders in fruit-growing regions is only suggestive; and a more exact investigation would be interesting.

Discussion

These organophosphorus compounds have been shown to inhibit cholinesterase irreversibly (Adrian 1947); and in man they produce characteristic effects, attributable to the depression of cholinesterase activity in the tissues. in addition to the usual muscarinic and nicotinic effects of cholinergic drugs, central-nervous-system symptoms have been seen after administration or exposure and found to be accompanied by easily recognisable E.E.G. changes (Grob and Harvey 1949, Rowntree, Nevin, and Wilson 1950, Grob, Garlick, and Harvey 1950).

In assays of tissues from laboratory animals poisoned with these compounds a rapid decrease of cholinesterase activity is observed coincidently with the rapid appearance of symptoms. In vitro, parathion combines relatively slowly with the cholinesterase enzymes of human tissues; and this combination, though reversible for several hours, subsequently becomes irreversible (Grob 1950). The duration of symptoms and cumulative effects are fairly well correlated with the degree to which the cholinesterase-anticholinesterase combinations are reversible in vitro. The combination of dyflos (D.F.P.) with cholinesterase is completely irreversible after the first few minutes; hence in vivo, cholinesterase activity is probably restored only by slow regeneration of new enzyme protein over a period of weeks. On the other hand, the combination of parathion or ethylpyrophosphate (T.E.P.P.) with cholinesterase appears to be partly reversible for about the first twenty-four hours. It is probably that, after cholinesterase has been inactivated by ethylpyrophosphate, parathion, and malathion in vivo, cholinesterase activity is restored partly in the first twenty-four hours by some dissociation of the cholinesterase-anticholinesterase combination, and afterwards exclusively by regeneration of new enzyme protein.

Another important consideration in the production of effects on the central nervous system is the solubility of these substances in lipids. The acute effects of parathion on the central nervous system are considerable (Grob, Garlick, and Harvey 1950). By contrast, neostigmine has very little effect (Grob, Lilienthal, et al. 1947). Ethylpyrophosphate has much more effect than neostigmine, but less than dyflos, which has a powerful effect approaching that of parathion. It is possible that because of the high lipoid content of the central nervous system, the cholinesterase is more accessible to anticholinesterases.

In vitro, after repeated doses of any of these substances, the enzyme is irreversibly inactivated, which leads to cumulative poisoning. It is conceivable that repeated inhibition of cholinesterase and perhaps interaction with other cellular constituents over a long period might eventually lead to alteration in biochemical functions and pathological changes.

In the present study effects on the central nervous system have been produced by organophosphorus compounds. Hitherto only their ability to destroy cholinesterase has been described.

Although deaths from poisoning have been reported, no sequelæ in those surviving acute poisoning or chronic exposure have been recorded. But Koelle and Gilman (1946) and Hunt and Riker (1947) demonstrated persistent paralysis affecting particularly the hind limbs in dogs and cats after repeated sublethal doses of dyflos. Bidstrup et al. (1953) have reported residual paralysis in man after exposure to another organophosphorus insecticide, mipafox. The long latent period from last exposure to onset of paralytic symptoms which they and Petry (1951) noted is interesting. Barnes and Denz (1951) produced paralysis in hens with dyflos, triorthocresylphosphate (T.O.C.P.), and mipafox, and also observed demyelination in the peripheral nerves and spinal cord of the affected birds. There is evidence that inhibition of the pseudocholinesterase may produce the demyelination (Earl and Thompson 1952).

More relevant to the cases reported in our study is the observation by Bidstrup et al. (1953) that the paralysis seen by them was associated with repeated exposure to substances which irreversibly inhibit cholinesterase. These authors noted mental changes in both their cases which they attributed to the atropine which was given. Delusions and hallucinations were observed. But in view of our findings the mental changes observed by Bidstrup et al. may well have been due to organophosphorus compounds.

This impression is further strengthened by the work of Rowntree, Nevin, and Wilson (1950) who administered dyflos to 26 psychotics (17 schizophrenics and 9 manic-depressives) for periods of seven to thirty-seven days. In 6 schizophrenics the psychosis was activated, and in chronic cases the florid symptoms which had characterised the onset of the illness reappeared. This was not a form of delirium, and consciousness was not impaired. The changes persisted for some months after withdrawing the dyflos. In the manic-depressive group in general, mania was lessened and depression increased. Insomnia and increased dreaming were also induced. 10 normal subjects developed a very characteristic picture of depression, irritability, lassitude, and apathy, and they looked dejected and felt unhappy.

These findings are essentially similar to ours—i.e., that only two forms of psychiatric illness were induced—depressive and schizophrenic reactions. This indicates that these insecticides activated a tendency towards depression or schizophrenia. This effect appears to be brought about by the central action of these agents on cholinesterase. It is thus possible that the activation may be related to the anticholinesterase action of the drug on the brain. This effect contrasts with the improvement in schizophrenics produced by intravenous injections of acetylcholine, reported by Fiamberti (1946).

The E.E.G. changes described by Rowntree (1950) were similar to the changes in the 1 case on whom we performed an E.E.G.

Follow-up of our cases showed that the effects persisted for at least six months after exposure ceased, but almost all reverted to normal in twelve months.

The effects on the central nervous system produced by these compounds which have been shown to inhibit cholinesterase within the brain suggests that the acetylcholine-cholinesterase cycle plays a positive, though as yet undefined, role in central neural function.

It may be objected that our results are due purely to chance and that exposure and mental change are not correlated. It is true that our results have not been analysed statistically and that they are drawn from the

community at large. One group however was distinct (the greenhouse technicians) and in this section the number affected was 8 out of 10.

Summary

In 14 men and 2 women exposed for between one and a half and ten years to organophosphorus insecticides, schizophrenic and depressive reactions were observed, with severe impairment of memory and difficulty in concentration.

These insecticides irreversibly inhibit cholinesterase; after lengthy exposure, the enzyme can be re-formed only by synthesis.

The findings of a small field survey suggested that psychiatric disorders might be commoner in fruit-growing areas than in towns.

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POSTANÆSTHETIC DEATH FROM PHÆOCHROMOCYTOMA WITHOUT HYPERTENSION

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IN the following case, in which the patient died after anæsthesia, the cause was discovered only at necropsy.

Case-report

The patient, a thin, rather nervous, unmarried schoolmistress of 33, attended the casualty department of the Radcliffe Infirmary on June 24, 1959. Ten days previously pain had commenced in the left ring finger, where an extensive pulp infection had subsequently developed. The patient's temperature was 100·6°F, but she was apparently fit and did not admit to any previous symptoms or illnesses of note. She reported having "struggled" during a previous nitrous-oxide dental anæsthetic, but there had been no untoward sequelæ.

Operation

Atropine 0·6 mg. was administered subcutaneously. One hour later anæsthesia was induced with thiopentone, 300 mg.; nitrous oxide, oxygen, and a low concentration of trichlorœthylene were used for maintenance. The patient was supine throughout the anæsthetic. The total time required for the application of the tourniquet, the operation, dressings, and plaster was about 40 minutes.

After 10–15 minutes of anæsthesia the first abnormal signs appeared. Respiration became deep and rapid, and cyanosis developed. The blood-pressure did not change, but the pulse-rate increased to 140 a minute; the pupils became widely dilated and did not react to light. Administration of 100% oxygen at this stage did not improve the cyanosis.

Subsequent Course

10 minutes after the anæsthetic was discontinued the patient was very restless and complained of difficulty in breathing. Cyanosis persisted. The systolic blood-pressure was 140 mm. Hg and the pulse was 150 per minute and regular. The pupils were widely dilated and did not react to light; there was no neck rigidity; the tendon reflexes were generally diminished, and two small hæmorrhages were visible on the temporal side of the right optic disc. The lung fields were clear; the abdomen was soft and no masses were palpable.

During the following hour the patient remained conscious and well orientated in space and time. The blood-pressure fell to 120/85 mm. Hg, and the pulse-rate rose to 160 per minute. At this stage crepitations appeared at the right base, and some thin, watery, bloodstained sputum was produced. The patient continued to complain of difficulty in breathing and tightness in the chest; she now also mentioned some lower abdominal pain, similar to that of a menstrual period. There was no evidence of peripheral thrombosis, œdema, or localising signs in the central nervous system.

A provisional diagnosis was made of paroxysmal supraventricular tachycardia associated with right-lower-lobe congestion. Oxygen therapy was reinstituted, and 1 g. of procainamide was given intravenously without effect. This was followed by digitalisation (with digoxin).

After a further hour the general condition was little changed, but crepitations were now audible at both lung bases. Pulmonary embolism was suggested, although clinical confirmation was lacking. An alternative suggestion was atropine hypersensitivity, possibly associated with some pre-existing lesion. 100 mg. of hydrocortisone was given intravenously, without effect.

The patient's condition appeared to improve slowly during the following 3 hours. Her pulse-rate came down to 130 per minute, and the blood-pressure remained at 120/80 mm. Hg; but dyspnœa, abdominal pain, and pupillary dilatation persisted.

5½ hours after the anæsthetic the patient's condition deteriorated rapidly. Abdominal pain and dyspnœa increased; she became grossly cyanotic and pulseless, and the heart sounds became inaudible. Although good air entry persisted for several minutes, moist sounds suddenly appeared in all lung fields and the patient frothed at the mouth. Artificial respiration was performed, and nikethamide and adrenaline were injected into the heart. These measures were ineffective and the patient died at the end of the 6th hour after the anæsthetic.

Subsequent questioning of the patient's parents and physician revealed that she had suffered from attacks of headache, sometimes associated with faintness, and had been treated for migraine for 5 years.

Postmortem Findings

1. Extreme generalised pulmonary œdema with congestion. Frothy fluid was present in the bronchi, but there was no evidence of inhalation of vomit, or of pulmonary embolism. There was terminal collapse of the left lung and right base.

2. Slight dilatation of the heart with a little left ventricular hypertrophy.

3. Moderate acute cerebral œdema.

4. A phæochromocytoma of the right adrenal gland. Most of the cells of this tumour were polyhedral, but fusiform cells were present in a few areas. Pleomorphism was distinct only around the margins of zones of hæmorrhagic necrosis. The cells were large, with abundant cytoplasm, and sometimes appeared to run together into symplasmic masses. The nuclei were usually central, ovoid, or spherical, with a clearly defined nuclear membrane and nucleolus, and a fine chromatin net. Mitoses were rare.

5. Congestion of the endometrium.

Discussion

In 1935 Pincoffs, discussing the diagnosis of phæochromocytoma, stated: " The first [type] is found only at autopsy in a previously healthy and symptom-free individual who unexpectedly collapses and dies after a minor trauma, such as some simple surgical procedure." Since then there have been several reports of death following an anæsthetic in an undiagnosed case (Steen 1957, Apgar and Papper 1951, Crowther 1951, Swan 1951, Koonce et al. 1952, Harrison and Seward 1954, Henry 1954). The classical features of an " attack " or " crisis " may not be present (Alwall and Wulff 1948, Goodall and Symington 1953, Henry 1954). Spatt and Grayzel (1948), for example, observed that in nearly all cases of *malignant* phæochromocytoma the blood-pressure is normal, and McGarack et al. (1942) also concluded that hypertension and other signs of crisis are lacking when a malignant phæochromocytoma is present.

The present case is of considerable interest in that hypertension was not observed even though other manifestations of a typical " attack " were well-marked, and the tumour was histologically non-malignant. The presence of dyspnœa, tachycardia, peripheral vasoconstriction, and pupillary dilatation due to phæochromocytoma without significant elevation of the blood-pressure must be exceedingly rare and must, as in this case, cause considerable difficulty in diagnosis.

McCullagh and Ingel (1942) reported the case of a 19-year-old girl who had attacks of hotness and dizziness associated with profuse sweating, trembling, palpitation, and coldness of the extremities. She was seen by three physicians, two of whom reported hypertension while the third found a normal blood-pressure. There were no true paroxysms of hypertension, although the basal metabolic rate was constantly raised. A highly cellular phæochromocytoma was removed, and hypertension developed during the operation when the tumour was manipulated. McCullagh and Ingel remarked: " Although the blood-pressure was variable, this variability was never shown to bear any relationship to her symptoms, for it was repeatedly found to be normal during an attack of sweating, and on several occasions was found to be high when she was feeling well and no attack was present."

In the present case the induction of general anæsthesia would not have prevented the occurrence of hypertension (Wadsworth 1955) since, as is well known, hypertension can occur during the manipulation of phæochromocytoma under general anæsthesia (Apgar and Papper 1951) and any slight fall in blood-pressure resulting from premedication or the administration of an intravenous barbiturate may be sufficient to " trigger off " a hypertensive episode.

" False positive " and " false negative " results may be obtained from the rogitine test after sedative and antihypertensive drugs have been administered (Roth 1960). Thus, the previous use of drugs may have prevented hypertension from developing: our patient suffered from migraine, and according to her family doctor she was worried about some school examinations at the time of her operation. It is therefore probable that she was taking considerable quantities of phenobarbitone and ergotamine tartrate, for which she had prescriptions. Hypertensive episodes in patients with phæochromocytoma are generally believed to be due to the periodic discharge of large amounts of adrenaline and noradrenaline from the chromaffin cells of the tumour (Millar 1957); the possible role of ergotamine tartrate as an anti-adrenaline compound is particularly interesting in this connection.

Summary

A 33-year-old woman died shortly after incision of a septic finger under general anæsthesia. Terminally the patient had dyspnœa, tachycardia, peripheral vasoconstriction, and pupillary dilatation.

A phæochromocytoma was found at postmortem examination.

Despite the presence of many of the classical features of a phæochromocytoma " crisis ", the patient's blood-pressure never rose above 140/80 mm. Hg. For some years the patient had been taking ergotamine tartrate as a remedy for migraine, and the absence of hypertension may have been related to this fact.

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FŒTAL HÆMORRHAGE INTO THE MATERNAL CIRCULATION

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WE here report an accidental fœtomaternal " transfusion ", large enough to require urgent treatment, in which, for the first time in this condition, fœtal erythrocytes were demonstrated in the mother's blood.

Case-history

A primigravada, aged 32, had a normal uneventful pregnancy of 40 weeks. On routine blood examination at the 32nd week, the hæmoglobin was 10·4 g. per 100 ml. and the blood-group A rhesus positive, and no antibodies were demonstrated. At term she was admitted to a maternity hospital for induction of labour because of slight pelvic deformity.

After medical induction had failed, a Drew-Smythe catheter was used to rupture the hindwaters. During this procedure about 30 ml. of bright red blood, with a small quantity of liquor, drained through the catheter. The fœtal heart-rate was 130 per minute. Labour started that evening and lasted until the next morning; after the second stage had lasted 2¾ hours, forceps were applied, using a pudenal block. A small amount of dark red blood drained during delivery.

The baby (weight 6 lb. 10 oz.) appeared normal after birth. He was a good colour and cried lustily; his heart-rate was 120 per minute. The placenta and membranes appeared intact, but they were not kept for detailed examination.

5 fœtal erythrocytes in the maternal circulation; the maternal erythrocytes appear as "ghosts".

3 hours after birth the baby was noticed to be breathing rapidly, and he had become pale. 2 hours later he was still very pale and very cold to touch; the rectal temperature was 90°F. At no time was he cooled; indeed, he had been kept warm in his cot by hot-water bottles. The baby was transferred to another hospital, with a sample of the mother's blood. On admission, 6 hours after birth, he had œdema of hands, feet, and scrotum; the rectal temperature was 91°F, pulse-rate 62 per minute, and respiratory rate 30 per minute. There was no evidence of internal or external hæmorrhage.

The possibility of neonatal "cold injury" was discounted because there was no history of accidental cooling, the baby having been kept in warm surroundings. Moreover, in primary cold injury the appearance in the early stages is not of pallor but of a ruddy colour.

The baby's blood was examined soon after admission. The hæmoglobin was 9·2 g. per 100 ml. The blood-film showed much anisocytosis, the cells being orthochromic; 65 nucleated red cells were counted per 100 white cells. The blood-group was A rhesus positive, with no evidence of ABO incompatibility, and the Coombs test was negative.

The baby was very slowly warmed in an incubator, and a slow transfusion of 100 ml. of group-O rhesus-positive blood was given through the umbilical vein. He progressed well and was discharged home 3 weeks later.

A blood sample (taken into sequestrene as anticoagulant) had been obtained from the mother 5 hours after delivery, and 5% of fœtal hæmoglobin was found (Singer "1-minute" method). Fœtal erythrocytes were demonstrated in methanol-fixed blood smears (see figure) from the bottled specimen, using the technique of Zipursky et al. (1959). 500 erythrocytes were counted on the suitably treated blood-films (see below), and 4% of the erythrocytes were fœtal, the rest being adult. The mother showed no untoward reaction to the fœtomaternal transfusion.

Discussion

Fœtal hæmorrhage into the maternal circulation has been demonstrated in the past by using the technique of differential agglutination of the fœtal cells, and by measuring the level of fœtal hæmoglobin in the maternal blood. Previous workers (Chown 1954, 1955, Colebatch et al. 1956, Borum et al. 1957, Gunson 1957, Shiller 1957, Goodall et al. 1958, McGovern et al. 1958, Weiner et al. 1958, Krivit et al. 1959, Nevanlinna 1959, Pearson and Diamond 1959) have used one or both of these methods; Chown and Krivit et al. measured in addition the rise in the anti-D titre in the mother's blood.

In 1959 Zipursky et al. used a technique, adapting an observation of Kleihauer et al. (1957), to distinguish adult from fœtal erythrocytes in a blood-smear. Fœtal erythrocytes are easily distinguishable in fixed films treated with an acid buffer at pH 3·4 because they resist lysis by the buffer solution and thus later react with hæmoglobin stains, whereas adult erythrocytes appear only as "ghosts". This has an advantage over the differential agglutination technique in its ease and speed, and over the chemical method in its greater accuracy when the fœto-maternal transfusion is relatively small, as is usual. The test should be applied within 12 hours of a suspected fœtomaternal transfusion, in case there is incompatibility between the mother's serum and the fœtal erythrocytes.

Cause of Fœtomaternal Transfusion

We presume that the fœtomaternal transfusion in this case was the result of damage to the placenta caused by the Drew-Smythe catheter. Russell et al. (1956) quote two cases in which the babies died after injury to the fœtal circulation through membrane puncture. Our case supports Russell's suggestion that, whenever blood is obtained at artificial rupture of the membranes, the fœtal hæmoglobin should be estimated in that blood. It also seems advisable to examine the mother's blood for fœtal erythrocytes whenever there is a possibility that the fœtal circulation may have been damaged, with or without revealed hæmorrhage.

The possible effects of fœtomaternal transfusion on the mother have been discussed (Chown 1955, Blair 1961), and these will be the subject of a further paper (Mr. B. E. Blair and Dr. I. F. MacMath).

Diagnosis

Fœtomaternal transfusion should be suspected if blood is obtained with membrane puncture, if the newborn baby develops obvious anæmia unexplained by other disorders, or if the mother shows symptoms (e.g., rigors) that might be attributable.

In such cases we suggest that the following investigations should be performed:

1. A test for fœtal hæmoglobin in blood lost in revealed accidental hæmorrhage.

2. Examination of the maternal blood for fœtal erythrocytes by the acid-lysis test, and later by agglutination reactions. A practical precaution easily taken is to collect a few blood-films from the mother without delay, because of the possibility of isoimmune destruction of fœtal cells, with the loss of valuable early evidence. These slides should be fixed in methyl alcohol, and can be examined at any time.

3. After the baby is born the blood-group should be determined if fœtomaternal transfusion has occurred. If the baby's cells are incompatible with the mother's serum, this information may be important in deciding (*a*) whether the transfused cells will soon cease to be detectable in the mother's blood, and (*b*) whether the mother has received a transfusion of incompatible blood.

Summary

In a case of fœtal hæmorrhage into the maternal circulation, fœtal cells were demonstrated in the mother's blood.

Trauma to the placenta by a Drew-Smythe catheter was the probable cause.

Suggestions are made for the investigation of cases in which fœtomaternal transfusion is suspected.

Our thanks are due to Dr. I. F. McMath and Mr. B. E. Blair for their cooperation; and to Dr. A. B. Raper for helpful advice.

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BIOCHEMICAL CONFIRMATION OF COLLAPSE DUE TO ADRENAL FAILURE

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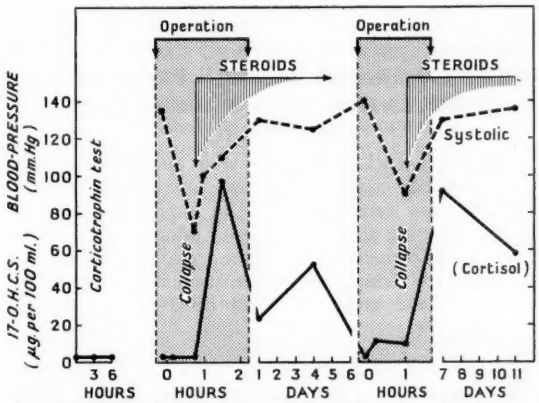
COLLAPSE under operative or other stress due to adrenal failure following steroid therapy is now well recognised (Salassa et al. 1953, Slaney and Brooke 1957). The condition is, however, a clinical concept based on circumstantial evidence—hypotension with no other cause such as blood-loss to account for it, and the restoration of normal pressure through the administration of hydrocortisone and not due to other measures. Confirmation that such episodes are attributable to adrenal failure can come only from a study of plasma-cortisol levels during collapse, and, apart from one plasma estimation in a possible case reported by Marks et al. (1959), as far as we are aware none have been recorded hitherto. The following case provides this confirmation:

A 25-year-old man was admitted to hospital with Crohn's disease of the large intestine. He had received prednisone 5 mg. b.d. for six months; this was discontinued just before admission. He showed none of the facies of hypercortisonism; his blood-electrolyte levels were normal. A routine corticotrophin test was performed on the day before exploratory laparotomy was undertaken without steroid cover. Shortly after the abdomen had been opened the blood-pressure fell from 135/80 to 70 systolic. At that time no appreciable bleeding had occurred; 50 mg. of hydrocortisone was therefore given intravenously in one dose and a further 50 mg. added to an intravenous saline infusion instituted before operation. Within five minutes the systolic pressure began to rise; at thirty minutes it had reached 100 mm. Hg; at sixty minutes it was 120 mm. The operation (hepatic and ileal biopsy) was completed during this period without further incident, and post-operative steroids (cortisone and corticotrophin) were gradually withdrawn over the next few days.

On the sixth postoperative day abdominal dehiscence necessitated further operation; again no steroid cover was given,



reliance being placed upon intravenous administration of hydrocortisone should collapse occur. The blood-pressure fell to 90 systolic during the operation; 50 mg. hydrocortisone was given with restoration of blood-pressure.

Estimations of plasma-cortisol levels, by a modification of the method of Silber and Porter (1954), were obtained during and after both operations (see figure). In the resting preoperative state there was less than 5 μg. per 100 ml. (normal between 5 and 30); there was no response to 25 units of corticotrophin intravenously (normal response 20–90 within three hours). There was therefore neither evidence of adrenal corticoid output at rest nor reserve to respond to the stimulus of corticotrophin; this state persisted until operation, the stress of which induced collapse. Restoration of serum levels through hydrocortisone administration was accompanied by a return of blood-pressure to normal, a similar correlation being observed during the second operation. Since no other factors, such as blood or fluid loss, had occurred, this case fulfilled the clinical picture of adrenal collapse; cortisol estimations throughout the period confirmed this. The case thus establishes biochemically the clinical concept of adrenal failure during stress.

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". . . there is, in the minds of the sisters, whether consciously or not, a significant connection between what she feels about those set over her and what she feels towards those put in her charge. It is no daring step to suggest that what she feels about the integration of the student nurse also colours her attitude towards the patients in her ward; both depend upon the extent to which she feels part of the system by which the senior staff at the hospital set out to understand the problems of those who not only serve at the bedside, but lie in the bed itself. No doubt the relation between doctor, nurse and patient is so apparently obvious that few have paused to ask precisely what it is, and upon what assumptions the existing systems of hospital organisation are based; it may be that an ethic of clinical command, simple and austere, assuming as a natural law the immediate compliance of the subordinate, has for too long obscured the labyrinthine complexity of what in fact underlies effective co-operation in the hour of emergency."—Prof. R. W. REVANS, Measurement of Supervisory Attitudes (read at meeting of Manchester Statistical Society, Jan. 11, 1961); p. 29. (Obtainable from the hon. secretary of the society, F.S.D. Ltd., 6, St. James's Square, Manchester, 2. 7*s.* 6*d.*)

Preliminary Communications

ENCEPHALOPATHY IN MICE PRODUCED BY INOCULATION WITH SCRAPIE BRAIN MATERIAL

SCRAPIE is a subacute progressive encephalopathy, of undetermined cause, occurring naturally in sheep.[1] Hadlow [2] has called attention to similarities between scrapie affecting sheep, and kuru,[3] affecting man; there has been no corroboration [4] of the report that scrapie is a myopathy.[5 6] Scrapie can be experimentally reproduced in sheep [7] and goats, [8 9] using cell-free filtrates [10] as inocula. There are no reports of successful transmission of scrapie to laboratory animals.

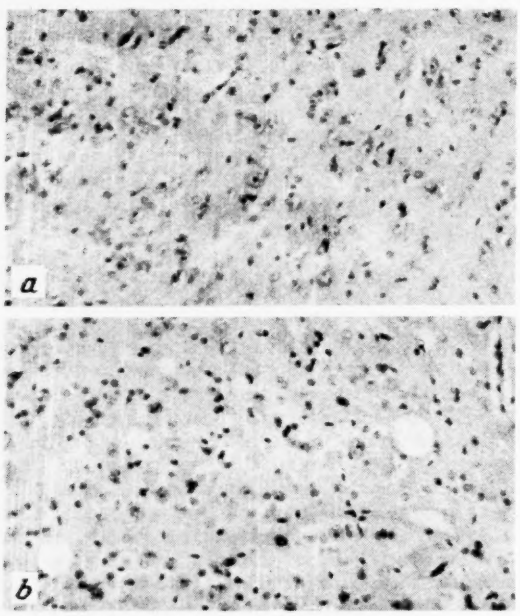

Fig. 1—(*a*) Normal mouse brain. (Hæmatoxylin and eosin.) (*b*) Affected mouse brain—corresponding area—showing vacuolation. (H. & E.)

Because recent studies at this institute demonstrated a difference in susceptibility to a bacterial infection in three different breeds of mice,[11] it was decided to inoculate mice of these breeds with scrapie brain material and to observe them over a long period. Pattison and Millson [12] have described two syndromes in scrapie-affected goats—one characterised by scratching, and the other by drowsiness and incoordination. They have suggested that these two forms of scrapie are reproducible in goats by sub-inoculation with appropriate tissue. In this present investigation inocula for mice were prepared from goat brains supplied by Mr. I. H. Pattison; one goat was affected with the "scratching" type of scrapie and one with the "drowsy" type, and a normal goat served as control.

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DETAILS OF MICE INOCULATED

Inoculum	Mouse breed	When inoculated	No. inoculated	No. of deaths within $7^1/_2$ months	No. showing nervous symptoms at $7^1/_2$–9 mos.
"Drowsy" type scrapie brain	C.57	Unweaned	18	1	0
		Weaned	17	1	0
	C.B.A.	Unweaned	21	5	0
		Weaned	20	0	0
	Swiss	Unweaned	16	10	0
		Weaned	20	8	8*
"Scratching" type scrapie brain	C.57	Unweaned	23	9	0
		Weaned	20	2	0
	C.B.A.	Unweaned	24	5	0
		Weaned	20	1	0
	Swiss	Unweaned	21	5	0
		Weaned	20	3	0
Normal brain	C.57	Unweaned	13	4	0
		Weaned	17	5	0
	C.B.A.	Unweaned	20	3	0
		Weaned	19	0	0
	Swiss	Unweaned	17	4	0
		Weaned	19	0	0

* Nervous symptoms as described in text.

MATERIALS AND METHODS

Mice.—Three breeds of mice were used: C.57 black, C.B.A. brindle (the foundation mice of both these stocks came from the Medical Research Council Radiobiological Unit, Harwell, by courtesy of Dr. M. F. Lyon), and Swiss white mice (from a closed population maintained at this institute for several years). Inoculations were made into unweaned mice of 1–4 days old, and into weaned mice of 3–6 weeks old.

Inocula.—10% w/v suspensions of each brain were prepared by grinding the tissue in a mortar together with sand and the appropriate amount of saline; this suspension was then centrifuged at moderate speed, and the opalescent supernate, freed of sand and gross particles, constituted the inoculum. Inoculation was made intracerebrally, the weaned mice being given about 0·03 ml., and the unweaned mice about 0·01 ml.

RESULTS

During the first $7^1/_2$ months of the experiment, which started in July, 1960, individual mice died at various

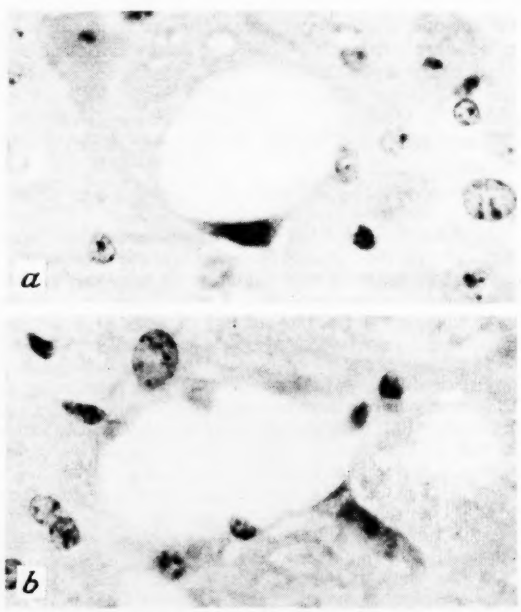

Fig. 2*a* and *b*—Vacuolated nerve cells. (H. & E.)

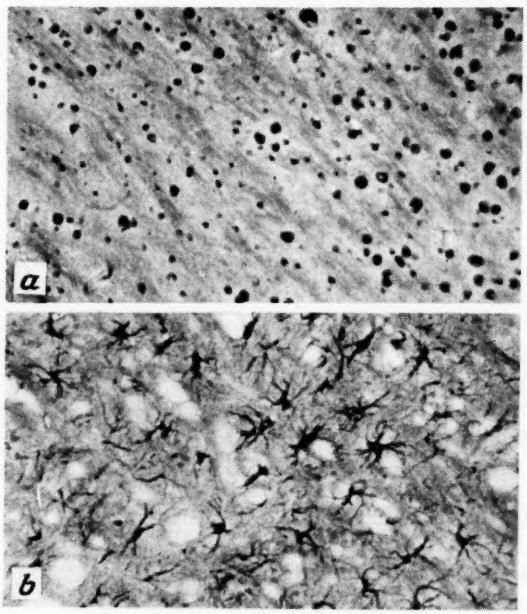

Fig. 3—(*a*) Normal mouse brain. (Cajal.) (*b*) Affected mouse brain —corresponding area—showing astrocytosis. (Cajal.)

intervals. There was little to suggest a single cause of death in any group, but it will be seen from the table that most deaths were among the Swiss mice inoculated, when unweaned or weaned, with the " drowsy " type of scrapie material. One of these mice was killed 7 months after inoculation, and histological examination of the brain showed changes resembling those to be described below.

7½ months after inoculation the first symptoms definitely suggesting neurological involvement were seen in one mouse. In the next 6 weeks seven more mice showed similar symptoms; all eight were members of the same group—i.e., weaned Swiss white mice inoculated with the " drowsy " type of scrapie brain. In this group, twenty mice were originally inoculated, and twelve had survived when the first case showed neurological symptoms. Thus eight of the twelve surviving mice have shown these symptoms; of the four others, one died and was unsuitable for examination, and three are suspect and still under observation.

The *symptoms* suggested disorder of function of the motor nerves, especially those associated with the hind quarters and tail. The mice stood with their hindquarters lowered close to the ground, and they were reluctant to move. The hind legs were occasionally dragged, the mice eventually walking with a stiff and rolling gait. The tail was held in an unnatural manner—stiffly and often to one side. If curled over a finger, the tail often retained a circular form for several minutes. When held up by their tails affected mice usually brought their hind feet together, whereas normal mice usually splay their hind legs. Some of the affected mice had ruffled coats and arched backs. To obtain fresh tissue for histological examination and subinoculation, affected animals were killed within 2 weeks of the symptoms first being noted.

Histological examination of the brains of affected mice revealed constant abnormalities. Sections stained with hæmatoxylin and eosin showed a rather generalised spongy appearance caused by vacuolation of the ground substance. This vacuolation was noted in the region of the cerebellar peduncles, in the medulla oblongata, and in the brain-stem (fig. 1). The cytoplasm of some nerve-cells was also vacuolated (fig. 2). The neurons of some nuclei were pyknotic and shrunken. Sections stained by Cajal's gold-sublimate method showed considerable astrocytosis (fig. 3). Inflammatory changes of the type usually associated with encephalitis were not observed.

These histological lesions resemble those of scrapie, described by Hadlow.[1]

DISCUSSION AND SUMMARY

A degenerative disorder of the central nervous system was observed in mice inoculated with scrapie brain material. The disease occurred in one of three breeds of mice inoculated when weaned, and when one type of scrapie brain material was used. The fact that the disease was observed in only one of the three mouse breeds is noteworthy because Gordon [13] found a wide variation in susceptibility to scrapie among breeds of sheep. Other points of similarity to scrapie are the long incubation period, the clinical symptoms, and the histological lesions.

Although the relation of this encephalopathy to scrapie requires further elucidation, these preliminary results are reported because they may be of interest to those studying degenerative conditions of the nervous system.

I wish to thank Dr. W. S. Gordon and Mr. I. H. Pattison for their advice, interest, and encouragement throughout this investigation; and Mr. F. Summerfield for the photomicrographs.

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PHENYLKETONURIA TREATED WITH A HIGH PHENYLALANINE INTAKE AND CASEIN-HYDROLYSATE/AMINOACID MIXTURES

IN the treatment of phenylketonuria the primary objective of maintaining the serum-phenylalanine within normal limits is achieved by restricting the intake of natural protein. The patient's nitrogen requirements are supplied by a mixture of phenylalanine-free casein hydrolysate with added aminoacids.[14 15]

This investigation was undertaken because a phenylketonuric boy, treated by the established method, was found to have a normal serum-phenylalanine level while receiving the aminoacid mixture, even when the additional protein intake had been raised to 1·5 g. per kg. per day. Not until the additional protein reached 2·3 g. per kg. (phenylalanine 120 mg. per kg.) did the serum-phenylalanine rise above 10 mg. per 100 ml., and phenylalanine and its abnormal metabolites reappear in the urine. This suggested that the mixture might have a specific effect independent of its low phenylalanine content. The mixture used (mixture I) was ' Cymogran ' (Allen & Hanburys), consisting of acid hydrolysed casein (nitrogen 11·5%) 40 g., L-tyrosine 2·5 g., DL-tryptophane 0·8 g., DL-methionine 0·5 g., carbohydrate, fat, minerals, &c., to 100 g.

THE STUDY

First Part

CASE 1, the boy in whom the original observation was made, was an inpatient at the National Children's Hospital. He was

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TABLE I—SERUM-PHENYLALANINE (MG. PER 100 ML.) IN CASE 1

(1960)	On basic diet only (protein 2·3 g. per kg.)	With aminoacid mixtures added to basic diet
Feb. 16	31·0	..
,, 18	31·0	..
,, 22	33·3	..
,, 25	..	25·0 } Mixture I (N×6·25 = 3 g. per kg. per day)
March 1	..	17·5 }
,, 3	..	23·0 }
,, 7	..	25·0 }
,, 12	38·0	..
,, 15	38·0	..
,, 18	39·0	..
9-day break		
March 30	..	22·0 }
April 1	..	24·0 } Mixture I
,, 5	..	24·0 }
,, 7	..	30·0 }
,, 12	..	30·0 } Mixture II (N×6·25 = 6 g. per kg. per day)
,, 16	37·5	..
,, 19	37·5	..
,, 22	..	26·0 }
,, 25	..	27·5 } Mixture I
,, 27	..	28·0 }
Mean ± S.D.	35·6625 ± 3·3166	25·166 ± 3·873

Standard deviation of the difference = 1·578; $t = 6·65114$; $P < 0·001$.

aged 6; his I.Q. was unmeasurable on the Terman-Merril (T.M.) scale; he had tow-coloured hair which darkened on treatment; and the serum-phenylalanine before treatment in November, 1959, was 31 mg. per 100 ml.

In September, 1958, when admitted to a mental-defective institution from a local-authority hospital, his weight was 32 lb. He lost weight on the ward diet (protein content unknown), but improved when given additional egg and milk (about 15 g. protein) and regained weight to reach 32 lb. in March, 1959. After a staphylococcal infection his weight again fell, and at the start of the low-phenylalanine diet, on Nov. 1, it was 28 lb. For dietary purposes his weight was taken to be 15 kg.

Apart from a break of 9 days, during which a low-phenylalanine diet was resumed, this boy was maintained for 10 weeks from Feb. 13, 1960, on a diet of 2·3 g. protein per kg. and 110 calories per kg., with vitamin supplements as for a low-phenylalanine diet. During this period mixture I, or a mixture of the hydrolysate and aminoacids in the same proportions, was given in intermittent courses of 15, 16, and 8 days. The dose of mixture I was 135 g. daily (N × 6·25 = 3 g. per kg. per day), made with 135 ml. of fresh lemon juice. The results are shown in fig. 1 and table I.

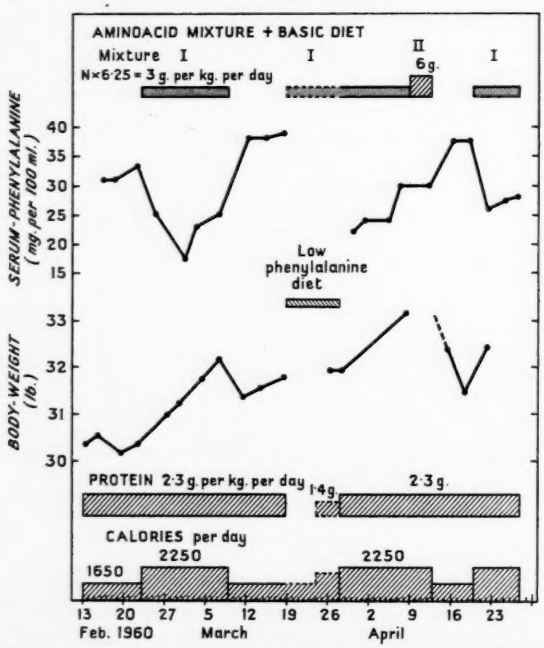

Fig. 1—Case 1: effect of aminoacid mixtures (see text) on serum-phenylalanine levels and body-weight.

When the mixture was started the serum-phenylalanine fell rapidly, and when the mixture was continued it tended to rise slightly, but when the mixture was stopped it rose abruptly.

The effect was greatest the first time—i.e., a week after the serum-phenylalanine had first regained its pretreatment level after a long period of low-phenylalanine intake.

For 4 days (from April 9–12), instead of mixture I, a mixture of the hydrolysate and aminoacids only was given in twice the previous dose (mixture II), with added glucose to keep the carbohydrate intake constant. No further change in serum-phenylalanine was produced, and as soon as mixture II was stopped it rose abruptly.

Over the whole period the serum-phenylalanine levels with the mixtures were significantly lower than with protein alone. Moreover, the changes in serum-phenylalanine on addition or withdrawal of the aminoacid mixtures, were always accompanied by an inverse change in body-weight. But the weight changes with change in nitrogen intake were of the same order irrespective of whether protein or aminoacids had been added or withdrawn.

TABLE II—SERUM-PHENYLALANINE (MG. PER 100 ML.) IN CASES 2 AND 3

	Case 2		Case 3		
(1960)	A (ward diet only)	B (mixture III added to ward diet)	C (mixture I added to ward diet)	D (ward diet only)	E (mixture III added to ward diet)
March 3	..	..	..	27·5	..
,, 7	..	..	..	28·3	..
,, 10	14·0	..	..	30·0	..
,, 22	16·0	..	..	28·0	..
,, 24	20·5	..	20·0	..	..
,, 26	16·5	..	20·0	..	..
,, 28	16·0	..	17·5	..	..
April 1	18·5	..	19·0	..	..
,, 5	15·5	..	..	28·5	..
,, 8	15·5	..	..	24·5	..
,, 19	16·5	..	..	27·0	..
,, 21	18·8	..	..	25·0	..
,, 23	..	13·6	..	..	26·0
,, 26	..	10·6	..	..	20·0
,, 28	..	9·2	..	..	20·0
,, 29	..	10·3	..	..	21·0
May 2	17·75	..	..	30·0	..
,, 5	17·0	..	..	28·0	..
Means	16·87	10·925	19·125	27·68	21·75
Standard deviations	1·852	1·881	1·153	1·803	2·87

S.D. of A and B = 1·091; $t = 5·45$; $n = 14$; $P < 0·001$.
S.D. of C and D = 0·934; $t = 8·590$; $n = 12$; $P < 0·001$.
S.D. of D and E = 1·2649; $t = 4·703$; $n = 12$; $P < 0·001$.

Second Part

Two adult phenylketonurics were studied in a hospital for mental defectives:

CASE 2 was a woman of 26, with brown hair, I.Q. 25 (T.M.), height 5 ft. 1 in., and weight 98 lb. (clothed).

CASE 3 was a woman of 19, with red hair, I.Q. 33 (T.M.), height 5 ft., and weight 91 lb. (clothed).

Serum-phenylalanine estimations were made frequently from the beginning of March, 1960. The patients were not weighed regularly, but over 6 months the weight of case 2 remained unchanged and case 3 gained 3 lb.

From March 23 to April 1 case 3 was given mixture I (made with lemon juice) 150 g. daily (nitrogen 7·9 g.) for the first 7 days, and 210 g. (nitrogen 11 g.) daily for the last 3 days. Case 2 was given 150 ml. lemon juice daily.

From April 22 to 29 cases 2 and 3 were both given daily a mixture of casein hydrolysate 60 g., L-tyrosine 3·75 g., DL-tryptophane 1·2 g., and DL-methionine 0·75 g. (mixture III). The mixture for case 2 was made with lemon juice, and that for case 3 with water.

The mixtures were given three times a day after meals, and the patients continued on the hospital diet which was rich in

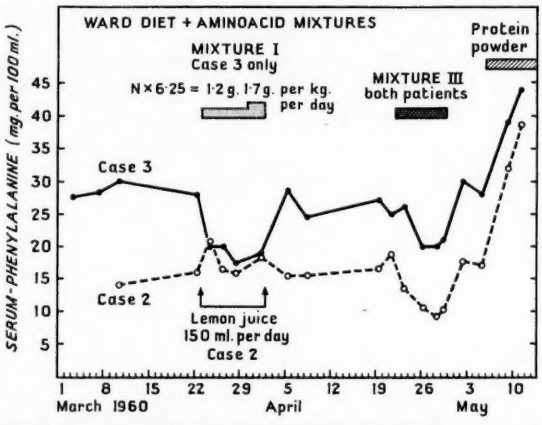

Fig. 2—Cases 2 and 3: effect of aminoacid mixtures (see text) and concentrated protein powder on serum-phenylalanine levels.

carbohydrate and contained 45–55 g. protein per day—of which almost half was first-class protein. The results are shown in table II and fig. 2.

The administration of either mixture was accompanied by an equally significant fall in the serum-phenylalanine level. The level was not further decreased by the larger dose of mixture I. The lemon juice had no effect.

From May 6 both patients were given a concentrated protein powder (' Casilan ', Allen & Hanburys) in a dose of 60 g. daily, in addition to their ordinary diet. This caused much increase in the serum-phenylalanine; while it was maintained at the higher levels case 2 was given tyrosine, tryptophane, and methionine for 8 days, and case 3 was given the hydrolysate alone for 5 days, followed by mixture III for 5 days. Both patients showed a slight downward trend in serum-phenylalanine, but in neither was the fall significant.

Third Part

More recently the three aminoacids only, and the hydrolysate alone and with various combinations of the aminoacids, have been given to cases 2 and 3 and to other patients. The results were inconclusive. The full mixture seems to be more effective than the hydrolysate alone, but no one of the added aminoacids can be regarded as more important than the others.

Methods

Blood was taken at the same time each day in relation to meals. Serum-phenylalanine was estimated chromatographically by the method of Berry,[16] but using 10 × 10 in. papers, and an overnight run, and with additional serum spots to give reference points at intervals of 0·7–3·6 mg. per 100 ml. for visual comparison with standards. Comparison by a densitometer was found to be unsatisfactory. At least three papers were run for each specimen. Because of the limitations of the method, changes in phenylalanine content, however great, were accepted as significant only if the sets of reference points used in the estimations did not overlap. Since the serum-phenylalanine fluctuates considerably, especially when the protein intake is not controlled, a fall in the level was not ascribed to treatment unless it was followed by an abrupt rise.

The phenylalanine content of foods was taken to be 5% of their protein content. In the diet of case 1 all items were measured, and their phenylalanine content was estimated, but the figures given for his protein intake include only that from the added milk and eggs.

DISCUSSION

Examination of the urines of all three patients by qualitative chromatography and the ferric-chloride test indicated a decreased excretion of phenylpyruvic acid, *o*-hydroxyphenylacetic acid, and phenylalanine, which coincided with the decreased serum levels. It was not possible to perform nitrogen-balance studies.

The dramatic fall in serum-phenylalanine when mixture I was first given to case 1 encouraged the hope that the mixture contained some substance capable of accelerating the breakdown of phenylalanine. But the later findings suggest that the effect was due to the increased intake of aminoacids. Because doubling the dose of the aminoacid mixture did not increase its effect, and adding the mixture to an equivalent dose of the protein powder produced less fall in serum-phenylalanine, it seems that the protein was in fact exerting the same effect as the mixture; but removal of phenylalanine from the serum would, of course, be masked by the increased intake.

The weight record of case 1 (fig. 1) is unfortunately incomplete, and its interpretation is more difficult without nitrogen-balance figures because an increase in nitrogen intake was necessarily accompanied by an increase in calories which were mainly derived from the carbohydrate and fat in mixture I. Nevertheless, it suggests that the decrease in serum-phenylalanine coincided with increase of body protein.

Addition of the aminoacid mixture to the diets involved a twofold or more increase in nitrogen intake, and it seems that the retention of protein which would be expected, at least during the anabolic phase, must necessarily have resulted in the utilisation of some of the phenylalanine available in the serum, since the intake remained constant. On this basis one would expect the serum-phenylalanine curve to be roughly the inverse of the nitrogen-balance curve, and thus to vary according to the original nitrogen balance.

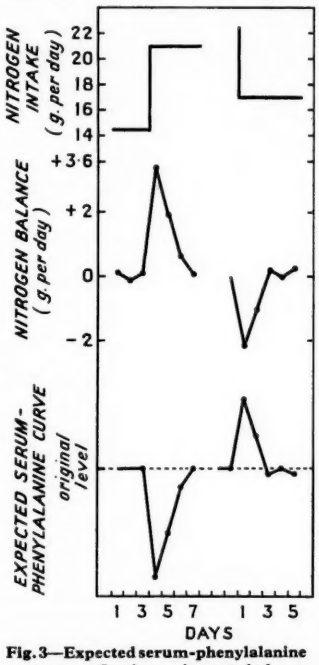

Fig. 3—Expected serum-phenylalanine curve reflecting nitrogen-balance changes on increasing and decreasing the intake of nitrogen (the phenylalanine intake remaining constant) in a patient originally in nitrogenous equilibrium.

Balance curves plotted from experiments by von Noorden, cited by Sherman.[17]

In a subject previously in nitrogenous equilibrium the serum-phenylalanine would be expected to fall abruptly on addition of the aminoacid mixture, reaching its lowest level on the 1st day of the anabolic phase, and thereafter rising within a few days to its previous level; on withdrawing the mixture the serum-phenylalanine should rise abruptly and again fall quickly to the original level. In a growing child, who responds to the increased nitrogen intake by an increased rate of growth and a greater positive balance, one would expect the serum-phenylalanine to fall initially and then to rise to a level lower than the

16. Berry, H. K. *Proc. Soc. exp. Biol., N.Y.* 1957, **95**, 71.

17. Sherman, H. C. Chemistry of Food and Nutrition; p. 182. New York 1911.

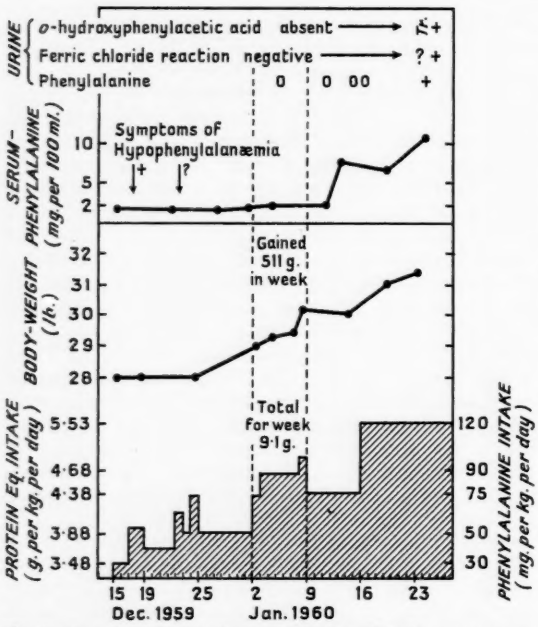

Fig. 4—Case 1: intake of nitrogen and phenylalanine necessary to induce weight gain and abnormalities in blood and urine after a low-phenylalanine diet.

The broken lines indicate the week chosen for comparison of flesh gained and intake of phenylalanine (see text).

original, there remaining constant until the rate of growth decreases. If the subject has previously been in a state of negative nitrogen balance, the phenylalanine in the serum must have been derived in part from the breakdown of tissue protein, and therefore one would expect the phenylalanine to remain at a lower level as long as the increased nitrogen intake maintained equilibrium or a positive balance. In all cases, however, the maximum fall is expected early in the anabolic phase, as in fig. 3.

If the serum-phenylalanine changes in cases 2 and 3 (fig. 2) reflect nitrogen-balance changes, they show that the positive balance, after the increased nitrogen intake, was sustained at its maximum for the whole of the 8 or 10 days during which the mixture was given. This would indicate that the patients were previously in a state of protein deficiency on an intake (about 50 g. per day) which should have been in excess of their safe practical allowances.[18] The fact that both patients were considerably under-weight for their age and height supports this conclusion, but it is unlikely that they were in a state of negative balance since they remained in good health and did not lose weight during 6 months on the ward diet.

However, the serum-phenylalanine changes may not merely reflect nitrogen-balance changes:

The four complete curves shown in figs. 1 and 2 do not correspond with the expected curve in that, though they all fall abruptly, they do not reach their lowest level for at least 7 days. In case 1, during the first 15 days of giving of mixture I, the serum-phenylalanine reached its lowest level on the 8th day and then rose steadily, though the rate of growth, as indicated by the weight change, remained constant. When the mixture was withdrawn the phenylalanine rose abruptly, with a corresponding fall in weight, but it continued to rise slightly even when increase in weight presumably indicated that the catabolic phase had ended. Thus the pattern of the curves indicates that initially the utilisation of phenylalanine was relatively greater than that of nitrogen, and suggests the possibility of a previous specific deficiency of phenylalanine.

Case 1 was grossly underweight for his age and failed to gain in the pretreatment year when receiving about 15 g. protein daily as well as a diet on which other children thrived. His progress on the low-phenylalanine diet is shown in fig. 4.

The fact that case 1 did not start to gain weight until the total nitrogen intake had reached the equivalent of nearly 4 g. protein per kg. per day would also suggest that his protein requirements were greater than those of a normal child, but this is of doubtful significance in view of the previous hypophenylanæmia. Nevertheless, the amount of phenylalanine ingested before the serum level rose above 10 mg. per 100 ml. is remarkable.

During the week Jan. 2–8 inclusive (fig. 4) the total weight gain was about 510 g., which represents the utilisation of 5·1 g. of phenylalanine, if we assume that 20% of the flesh gained was protein, of which 5% was phenylalanine. But the total intake of phenylalanine was 9·1 g., of which 10% may have been hydrolysed in the normal way, leaving a balance of 3·1 g. unaccounted for. This week is chosen because the weight gain was already well established, the patient was then physically and mentally at his best, the serum-phenylalanine had not risen above 2 mg. per 100 ml., and the urine remained free from phenylalanine and its abnormal metabolites for a further 2 weeks.

The assumption that the ingested phenylalanine was all utilised is not of course justified, for it takes no account of pathways of degradation of phenylalanine other than through phenylpyruvic acid, nor of possible excess fæcal loss of dietary protein, and the negative urine tests were not performed on 24-hour specimens. But the discrepancy is striking and again suggests the possibility that the ingested phenylalanine was being utilised to make good a specific deficiency of the substance. Theoretically such a deficiency is possible and an abnormally high-protein requirement is to be expected.

It is known that in phenylketonuria there are secondary disturbances in the metabolism of tyrosine [19] and tryptophane [20 21]; and other aminoacids may be similarly involved.

Bickis et al.[22] have shown that both the oxidation of tyrosine and its incorporation into protein are inhibited by excess phenylalanine or by sodium phenylpyruvate. Clearly this inhibition could, at a certain level of tyrosine intake, bring about such a deficiency of tyrosine at the site of protein synthesis as to inhibit in turn the incorporation of phenylalanine itself. But the inhibition of tyrosine can be overcome, at least in part, by increasing its availability; for pigmentation can be increased in those phenylketonurics in whom it is deficient by giving tyrosine.[23] Furthermore, in experimental phenylketonuria in monkeys, a dose of phenylalanine with tyrosine caused a smaller rise in the serum-phenylalanine than the same dose given alone.[24] This suggests that the excess tyrosine in some way assists the metabolism of phenylalanine.

It seems reasonable to suppose that inhibition, by phenylalanine and its abnormal metabolites, of the metabolism of other aminoacids might also be overcome by increasing their availability. Excess phenylalanine also directly inhibits its own incorporation into protein, and there is no evidence that this could be overcome by an excess of the component aminoacids. But it may be significant that excess phenylalanine does not inhibit its incorporation into lipids.[25]

18. F.A.O. Nutritional Studies, no. 16. Rome, 1957.

19. Cowie, V. A. *J. ment. Sci.* 1951, **97**, 505.
20. Armstrong, M. D., Robinson, K. S. *Arch. Biochem.* 1954, **53**, 287.
21. Pare, C. M. B., Sandler, M., Stacey, R. S. *Lancet*, 1957, i, 551.
22. Bickis, I. J., Kennedy, J. P., Quastel, J. H. *Nature, Lond.* 1957, **179**, 1124.
23. Snyderman, S. E., Norton, P., Holt, L. E., Jr. *Fed. Proc.* 1955, **14**, 450.
24. Waisman, H. A., Wang, H. L., Harlow, H., Sponholz, R. R. *Proc. Soc. exp. Biol., N.Y.* 1959, **101**, 864.
25. Haining, J. L., Fukui, T., Axelrod, B. *J. biol. Chem.* 1960, **235**, 160.

Therefore in phenylketonuria, I suggest that phenylalanine, by its high concentration in the serum and the presence of its abnormal metabolites, causes such a disturbance in the metabolism of other aminoacids as to lead to their relative deficiency and so indirectly to inhibit its own incorporation into protein. Below a critical level of protein intake these mutual inhibitions would lead to general protein depletion; but above such a level it is possible that they would lead primarily to a selective depletion only of those proteins with a high content both of phenylalanine and of any one or more of the other aminoacids involved in the disturbance. Therefore, in suggesting a deficiency of phenylalanine in the protein pool, it is not necessary to postulate the formation of unnatural proteins; nor is the suggestion in conflict with the findings of Block et al.[26] that the phenylalanine content of the total protein of several organs, including the brain, was not significantly different in a phenylketonuric and a normal control.

If the view here presented were shown on examination to have substance, it would confirm clinical impressions that a high intake of nitrogen is at least as important therapeutically as the maintenance of a normal serum-phenylalanine. Moreover, if the observed effect could be produced by a small group of aminoacids, they might conceivably provide an alternative form of treatment. Defective utilisation of aminoacids, including phenylalanine itself, could well account for the mental deficiency.

26. Block, R. J., Jervis, G. A., Bolling, D., Webb, M. *ibid.* 1940, **134**, 567.

I plan to investigate the findings further by repeating the experiments with nitrogen and phenylalanine balance studies, and by comparing the efficiency of utilisation of dietary nitrogen in phenylketonurics and normal controls.

SUMMARY

In three low-grade phenylketonurics, administration of casein-hydrolysate/aminoacid mixture, with an adequate but not a high protein intake, was accompanied by a small but significant decrease in serum-phenylalanine levels.

This finding might reflect an increased utilisation of phenylalanine of a greater degree than would be explained by the expected increased protein anabolism. Arguments are presented in support of the view that phenylketonurics having an amount of protein that would normally be considered adequate, either have a general protein depletion or a specific deficiency of phenylalanine, or perhaps both.

I am indebted to Mr. Thomas Dowling of this department, who did all the chromatography, and to Dr. John Fitzgerald for the intelligence tests.

I wish to thank Prof. Frank Kane for his patient encouragement; Dr. R. E. Steen, under whose care case 1 was treated, for generously allowing me access to his patients; the nursing staff of the Wicklow Clinic at the National Children's Hospital, and Miss Dempsey, the dietician: the Sisters of Charity of St. Vincent De Paul, and the nursing and medical staff at St. Joseph's Clonsilla and Holy Angels, Glenmaroon, where the remaining patients were studied: and Dr. H. E. Counihan for his constant help.

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Medical Societies

MANCHESTER MEDICAL SOCIETY

Export of Universities

AT a meeting of fellows on May 31, Sir ERIC ASHBY talked on the Export of Universities to Under-developed Countries.

He said that, by a process of natural selection among institutions of higher education, the university has survived and taken root all over the modern world, whereas other analogous institutions (e.g., the Islamic *madrasa* and the Japanese *daigaku*) have not adapted themselves to modern conditions. The adaptation of universities to societies which are not in the stream of European culture presents special problems; and he cited examples from tropical Africa.

Societies in tropical Africa respond to Western education in three successive phases. At first, the European is supremely confident that what he brings is " right " for Africans, whereas Africans are suspicious and hostile. Then Africans adopt unquestioningly the European pattern of education (as an instrument to achieve national aspirations) and are suspicious when Europeans propose any adaptation to suit African conditions. The third phase (just beginning in West Africa) is one in which Africans desire to turn Western education from being an alien implantation into something which is adapted and appropriate to African society.

In thinking about the adaptations which may be made as universities take root in Africa, we need to affirm one principle and to make three assumptions. The principle is that there can be no compromise about standards in university education; higher education is an international currency, and if a country wants a university it must be willing to maintain it on the gold standard of learning. The three assumptions to be made about a university in a tropical African country are: (1) that its purpose is to change, not to preserve, the indigenous culture; (2) that its aim is not at first to be supranational and cosmopolitan, but national, regional, even tribal; and (3) that higher education must develop at a pace far greater than the pace at which it developed in Europe. The consequences, for the university as an institution, of this principle and these assumptions, need very careful and lengthy study.

Reviews of Books

A Short Textbook of Hæmatology

R. B. THOMPSON, M.D., F.R.C.P., senior lecturer in medicine, King's College Medical School, University of Durham. London: Pitman Medical Publishing Co. 1961. Pp. 292. 30*s*.

THE postgraduate student of hæmatology is well catered for by large and comprehensive texts. The medical undergraduate is less fortunate: sections in general textbooks of medicine are on the whole unsatisfactory in the larger volumes and scrappy in the smaller ones. This is where Dr. Thompson's book comes in. It provides a readable account of the clinical features of blood diseases, and of their diagnosis and treatment, without going into more detail than is absolutely necessary. Laboratory techniques are not included at all. The author agrees that an " intimate knowledge " of the microscopical appearance of blood and marrow cells is still needed for accurate diagnosis in blood diseases, but suggests that practice is essential, and, for those who wish to practise, good atlases are available as guides; he includes four colour plates of rather indifferent quality to illustrate points in the text.

The text includes a remarkable amount of basic information about the properties and functions of red cells, white cells, blood-groups, the spleen, and so on. Good outline accounts of iron metabolism and the importance of vitamin B_{12} and folic acid are given. The hæmorrhagic diseases are given an excellent clinical description, and the basically important points about clotting factors are set out without recourse to complex diagrams showing the interrelation of the various factors. A section on disorders of the lymphoid tissue is included, and for Hodgkin's disease he follows the classification into granuloma, paragranuloma, and sarcoma. The chapter on myeloma includes some notes about macroglobulinæmia and allied diseases. A good account is given of myelosclerosis—a condition that seems to be more often diagnosed these days—and the differential diagnosis is fully explained. This book can certainly be recommended to the medical student who prefers several short books to one massive tome; it will provide him with all he needs to know about clinical hæmatology.

This is Your Child

The Story of the National Society for the Prevention of Cruelty to Children. ANNE ALLEN, ARTHUR MORTON. London: Routledge & Kegan Paul. 1961. Pp. 198. 25*s*.

THIS book tells the story of the N.S.P.C.C. from its foundation in 1884, and the emphasis on individual cases which the Society has dealt with makes it interesting and moving to read. Shortly after the Society was formed, shelters were opened for needy children, and a campaign began to change the law. This culminated in a series of Acts of Parliament between 1889 and 1904 which were designed to improve the lot and increase the rights of children. Other extending and consolidating Acts followed, and in all of them the Society played an important part.

Most people probably think of the N.S.P.C.C. as primarily a prosecuting agency. In fact, rather less than 2% of the cases coming to the Society's notice end in prosecution. "The backbone, the heart and spirit of the Society lie in patient remedial help to people who, either through a limited intelligence or a warped one, are unable to give their children the physical and emotional sustenance that is the birthright of every child."

Separate chapters are devoted to the subjects of neglect, physical cruelty, and mental cruelty, illustrated by case-histories. Problems of vagrancy (including Aldermaston marchers), canal-boat children, and children left alone at night are also discussed. Surprisingly, nearly three out of every ten cases dealt with by N.S.P.C.C. inspectors arise because people come to them for advice and not because someone has reported them.

The book reveals the grim results of the dismal philosophy of "keeping oneself to oneself" and not getting "mixed up" in anything. When one example of prolonged cruelty to a small boy was discovered, three neighbours stated that for months they had heard him screaming and begging his father not to hit him again—yet they had done nothing. An eight-year old girl was made to stand on a small square of bare earth from 8 in the morning till 6 at night for nine months on end, in frost, in rain, and in intense heat. She was seen by perhaps 30 or 40 adults: some of them passed her apples and biscuits; but none of them informed the N.S.P.C.C. inspector or any other social worker or the police. Some of the cases will shock those who are inclined to think that "such things couldn't happen in this country": they have happened and are happening. The fact that at least the grosser forms of cruelty are now less common is largely due to the N.S.P.C.C. and its inspectors and women visitors.

Western Psychotheraphy and Hindu Sâdhanâ

A Contribution to Comparative Studies in Psychology and Metaphysics. HANS JACOBS. London: George Allen & Unwin. 1961. Pp. 232. 35*s*.

CONVERSANT with the theories of orthodox psychoanalysis and at one time a pupil of C. G. Jung, Dr. Jacobs later became dissatisfied with what he regards as the limitations of both Freud and Jung. His interest in Hindu philosophy led him to make long visits to India, where he obtained instruction under spiritual guides, and he has found the concepts of Sâdhanâ (popularly known as Yoga) to transcend those of Western depth-psychology. Also, he has used Yogistic methods to supplement his psychotherapeutic techniques. This application of his studies is illustrated by five case-histories of patients treated by him in Australia.

The Western reader, immersed in a materialist civilisation, must be prepared to discard some of his preconceived "scientific" beliefs to follow the author's exposition of Hindu philosophy and the Sâdhanâ exercises, both mental and physical. He should then be grateful to have such an intelligent, erudite, and perceptive guide to the metaphysics and spiritual practices of one of mankind's most advanced cultures, as Dr. Jacobs proves himself.

He compares the psychological ideas of Freud and Jung with those of the Hindus, concluding that even Jung's aim of "individuation" is at best a means, not an end. "The individual as such cannot be nature's last aim."

The book has an index, but a glossary of Hindu terms would have been useful. There are many illustrations of patients' dream material.

The Tonsils and Adenoids in Childhood

DONALD F. PROCTOR, M.D., associate professor of laryngology and otology, Johns Hopkins University School of Medicine. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 70. 60*s*.

THIS is one of the pædiatric surgical monograph series, and it is written mainly for students and general practitioners. A rational list of indications for tonsillectomy is discussed; and it is emphasised that rewarding results will only follow careful preoperative assessment, meticulous surgery, and intelligent follow-up. The management of tonsillitis itself is not dealt with quite so fully as the surgical details. The risks of tonsillectomy are detailed with great care, and it is properly emphasised that all deaths and a large proportion of post-operative complications are avoidable. Max Brodel's beautiful drawings add distinction to an already elegant publication.

Fundamentals and Possibilities in Anti-tuberculosis Vaccination

RICHARD PRIGGE, M.D., professor and director; GUNTHER HEYMANN, M.D., professor and scientific member, State Institute for Experiment Therapy, Paul Ehrlich Institute, Frankfurt-on-Main. Translated from the German by H. Chandler Elliot. Toronto: Toronto University Press. London: Oxford University Press. 1961. Pp. 108. 40*s*.

THE first 48 pages of this monograph review the knowledge of resistance, immunity, allergy, and immuno-chemistry in tuberculosis. B.C.G. is dealt with in 22 pages. The definitive study carried out by the Medical Research Council, which provided unequivocal evidence of the protective effect of B.C.G. vaccination in a particular population, receives only 14 lines; and the criticism of this work by Meyers is apparently accepted as entirely valid. The book is a useful compilation from a vast literature; but many readers may think that the authors have failed to strike the right balance.

The Control of Disease in the Tropics (2nd ed. London: H. K. Lewis. 1961. Pp. 422. 47*s*. 6*d*.).—This book by Dr. T. H. Davey and Dr. W. P. H. Lightbody has been the authoritative text on tropical hygiene since its first edition in 1956. During the past five years the importance of pulmonary tuberculosis and poliomyelitis in the less developed countries has been increasingly recognised. And the big part that general measures of social betterment, water-supplies, roads, and health education have to play in the control of disease (even of communicable diseases, such as yaws, for which satisfactory cures are available) is also more widely appreciated. Meanwhile, the World Health Organisation's campaign for the eradication of malaria has progressed satisfactorily in some areas, but not at all in others. The second edition takes note of these trends, some of which its authors began. New chapters are devoted to poliomyelitis and health education, and those on malaria, leprosy, and tuberculosis have been modified. By skilful editorship, the length and price of the book have not been increased, and it can be welcomed unreservedly.

Electron Microscopy in Anatomy (London: Edward Arnold. 1961. Pp. 288. 50*s*.).—This volume records the proceedings of a symposium held in London in April, 1959, under the ægis of the Anatomical Society of Great Britain and Ireland. The contributions indicate clearly how vast is the expansion of the anatomist's horizons, and, in the words of the preface, "leave no doubt as to his special responsibilities in this field". The title of the book is somewhat misleading, for not all contributions are by anatomists, and most of the chapters are of fundamental interest to workers in all the basic medical sciences, including pathology, and to biologists. The editors are Prof. J. D. Boyd, Prof. F. R. Johnson, and Prof. J. D. Lever.

SYMPOSIUM ON ANTICOAGULANT THERAPY

Report of the Proceedings of the Symposium held at the Royal Society of Medicine on 18th and 19th November, 1960

Papers presented and discussed at the Symposium:—

A Review of the Action of Oral Anticoagulants on the Blood Coagulation Mechanism.

Anticoagulants and the Liver.

The Place of the Quick's One-Stage Test.

Laboratory Control of Anticoagulant Therapy.

Experiences with Thrombotest.

The Laboratory Control of Anticoagulant Therapy.

Treatment from a Pathologist's Point of View.

Experience with Fibrinolysin in the Treatment of Thrombo-embolic Disease.

Selection of Patients for Life-long Anticoagulant Therapy: Organization of Therapy of Large Groups of Patients.

Acute Coronary Insufficiency.

Long-term Therapy in Coronary Thrombosis.

An Evaluation of the Effect of Long-term Anticoagulant Therapy on the Prognosis of Coronary Artery Disease.

Indications for Anticoagulant Therapy in Peripheral Arterial Disease.

The Hospital Management of Long-term Anticoagulant Therapy.

Problems of Long-term Anticoagulant Therapy in Australia.

The General Practitioner Role in Anticoagulant Therapy.

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Anticoagulant Therapy in Cerebro-vascular Disease.

Pulmonary Hypertension and Mitral Valvular Disease in Relation to Anticoagulants.

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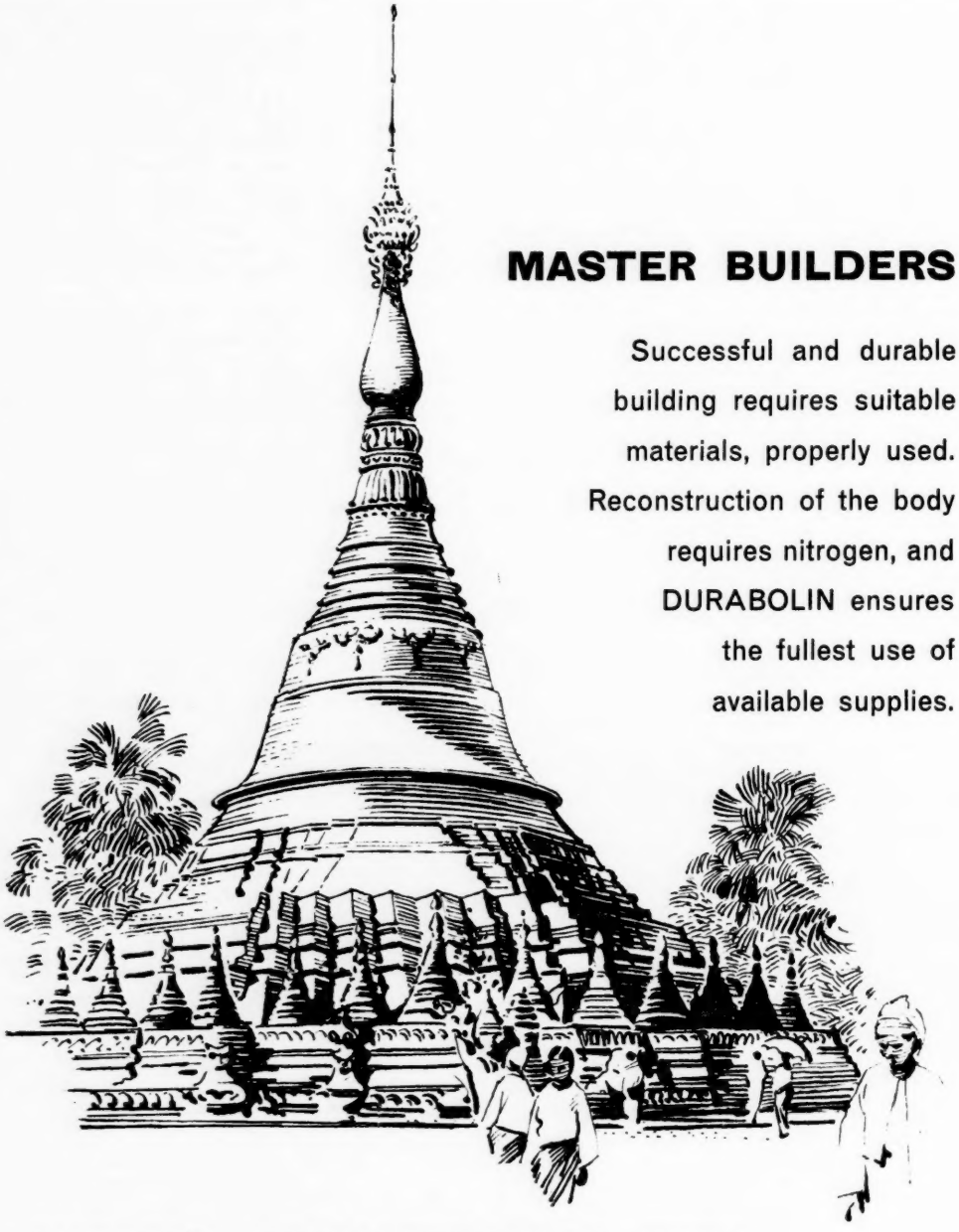

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THE LANCET

LONDON 24 JUNE 1961

Yet Another College?

IF there were a typographical symbol for a sigh we should feel inclined to use it in response to the news that some psychiatrists are urging their colleagues to set up yet another college. What are the reasons put forward in favour of this? It is held to be necessary to improve the status of psychiatry by establishing a higher qualification and ensuring the direct representation of psychiatrists in negotiations with the Government and on advisory appointments committees. The pros and cons of these individual aims could be debated at length, but it is more important to examine the presuppositions on which the idea of a college is based. The first is that psychiatry differs so much from the rest of medicine that unlike, let us say, cardiology or dermatology it needs a special organisation not merely to further its scientific aims, but to look after its professional interests—and it is significant that some psychiatrists actually speak of "the profession" of psychiatry. The second presupposition is that for lack of a college the prestige and material interests of psychiatrists suffer in comparison with those of other specialists. Some psychiatrists who do not advocate a college nevertheless share the general objectives of those who do.

In contrast to the Continental practice, British psychiatry grew up without university status and uniquely compartmentalised. It has its origins in the mental hospitals, and the establishment a hundred years ago of two special neurological hospitals set a gulf between psychiatry and neurology in this country which is still not completely bridged. Until about thirty years ago most psychiatry outside mental hospitals was done by neurologists, and only patients who could not be treated at home came under the care of psychiatrists. After the 1914–18 war there were several developments. The first English university chair in psychiatry was established at the Maudsley Hospital. By slow degrees consultant appointments in the subject were made at undergraduate teaching hospitals, and produced a group of psychiatric consultants who, though they had had mental-hospital experience, no longer practised in mental hospitals. Then the development of analytical psychopathology and psychotherapy received a great impetus from the war, and these disciplines were practised by yet another group of medical psychologists, usually unrelated to both the mental hospitals and the teaching hospitals, but attached to special hospitals, such as the Cassel, or outpatient institutes, such as the Tavistock Clinic. Hence, by the 1930s there were at least five different classes of doctor practising psychiatry in some form, not to mention those concerned with the assessment and care of mental defectives as they were then called; and an even larger number of bodies were concerned in one way or another with the interests of psychiatrists, including the Royal College of Physicians, the Royal Medico-Psychological Association, the Psychological Medicine Committee of the B.M.A., and the universities and the Conjoint Board which examined for the diploma in psychological medicine. At that time, there being little effective treatment for serious mental disorder, the work of the mental hospital was largely custodial, and psychiatry outside it was concerned either with diagnosis and disposal or with analytical or supportive psychotherapy.

In the past thirty years the situation has been completely transformed as the result of numerous interacting factors. First, and perhaps most important, is the advance of treatment. Electroshock therapy, leucotomy, and more recently the new pharmacotherapy have greatly shortened the stay of many patients in the mental hospital, and at the same time increasing provision is being made to care for the mentally sick in hostels, day hospitals, and their own homes. As a result it is estimated that in fifteen years the number of mental-hospital beds required will be about half of what it was in 1954. A major advance in our knowledge of the pathogenesis and treatment of schizophrenia might substantially reduce even this number. Parallel with this trend has been the establishment—though as yet on a far smaller scale—of psychiatric beds in general hospitals and of more professorial units in psychiatry in teaching hospitals. Quite recently the change in the social attitude to mental illness, which found expression in the report of the Royal Commission, has greatly reduced the legal red tape in which both patient and mental-hospital authorities in the past readily became involved.

Thus, the whole development of psychiatry during the last thirty years has been in the direction of closer integration with general medicine. The great advances in treatment have involved the use of physical methods; and research is increasingly directed to the study of disordered physiology, which is strikingly illustrated by the discovery of biochemical abnormalities as an important cause of mental subnormality. It is increasingly recognised that the psychiatrist in a general hospital has often much to contribute to the treatment of the patients of his general medical and surgical colleagues. For the reasons already given the barriers between the mental hospital and the general hospital are being progressively lowered, and this process is being greatly facilitated by the fact that all hospitals alike are part of a unified National Health Service. Extrapolating to the future, it may be predicted with confidence that it will not be long before the distinctions between psychiatry and the rest of medicine which have loomed so large in the past, and still influence some of the older members of the profession, not all of them psychiatrists, will be regarded as historical curiosities to a considerable extent peculiar to Great Britain.

Could there possibly be a less suitable moment to try and perpetuate these distinctions by establishing a College of Psychiatry? Rapid growth must always

involve tensions and necessitate adjustments. With patience these difficulties can be overcome, but not by an attempt to arrest the growth. King Canute got only his feet wet, because he was wise enough to move, but a College of Psychiatry would soon be submerged by the rising tide of medicine.

Prevention of Rh Hæmolytic Disease

THE discovery in 1941 of the role of the Rh factor in the pathogenesis of hæmolytic disease of the newborn [1] was followed by a search for means of preventing this disease. Three lines of approach are possible: (1) to prevent immunisation of Rh-negative women; (2) to "neutralise" or inactivate antibody already formed; or (3) to protect the fœtus from the effect of antibody. In fact, little has been achieved along any of these lines, and it has been in the treatment of the affected infant that progress has been greatest. Of affected infants who are born alive, up to about 95% survive with exchange transfusion.[2] But problems still exist in the management of infants who are desperately ill at birth and also sometimes in the control of hyperbilirubinæmia. The success of exchange transfusion has brought into prominence stillbirths due to this disease. At present the only accepted method of preventing these is premature delivery. Some time ago we suggested that, even if stillbirth could be reliably predicted, premature induction could at best prevent only half these deaths in utero since in many cases the fœtus died at an early stage of development. This is especially liable to happen in cases with the clearest indication for induction—namely, one or more previous stillbirths from this cause.[3]

Stalemate having been reached, it is not surprising that attention has shifted to the prevention of immunisation. Something has already been achieved in this direction by ensuring that Rh-negative women never receive Rh-positive blood by transfusion or intramuscular injection. Thus, although transfusion will cause the development of antibodies in 50% of individuals,[4 5] in the vast majority of instances immunisation results from pregnancy. But even with an Rh-negative mother and an Rh-positive fœtus, only about 1 in 20 mothers develop antibodies; and immunisation hardly ever occurs in a first pregnancy. Why should some women be immunised and others not? DIAMOND [6] suggested that the explanation lay in an individual variation in the ability to produce antibodies; and WIENER [7] believed that this difference had a hereditary basis—a view that was refuted by GERRARD and WATERHOUSE.[8] Similarly an explanation based on immunological tolerance was rejected.[9] Homozygous Rh-positive blood is a more potent antigen than heterozygous blood [10]; but, whereas this might account for the difference between different donor cells, it cannot account for immunisation by pregnancy, for in such circumstances the infant must be heterozygous. This presupposes the escape of fœtal red cells into the mother—a hypothesis originally postulated by LEVINE and KATZIN [11] on the ground that Rh substance does not exist in soluble form but is present only in cells. MURRAY [12] has shown that R_2 is more effective as an antigen than R_1, but in the process of immunisation this can play only a small part.

Two investigations of Rh hæmolytic disease have shown how further progress in management may be made by prevention rather than treatment.[13 14] Both investigations arise out of a series of earlier studies, and they are especially valuable in that, although the approaches are quite different, the results are complementary and the conclusions are similar.

One study, conducted in Newcastle, arises from a quantitative population survey based on the "complete" ascertainment of Rh hæmolytic disease in Northumberland and Durham. In their initial report KNOX and WALKER [15] measured the incidence of the disease and estimated the risk in infants at risk—i.e., second or later Rh-positive infants of Rh-negative mothers—at about 1 in 17. They stated that in ætiology a "genetic" factor could be distinguished from an "environmental" one by means of the birth-rank distribution of affected infants; and they concluded that the essential factor was not genetic but that it developed after marriage. NEVANLINNA,[16] in an analogous study in which the observed birth-rank distribution was different, reached the opposite conclusion. LEVINE [17] in 1943 first drew attention to the significant increase in ABO-compatible matings in mothers in whom Rh antibodies developed; and because of the large surface area of villi in the placenta, he assumed that fœtal red cells must escape into the maternal circulation in most pregnancies.[18] KNOX, MURRAY, and WALKER [19] studied the protection afforded by ABO incompatibility with special regard to the more specific mother/fœtus heterospecificity rather than that between husband and wife. By examining the ABO blood-groups of "first affected infants", their mothers, and the preceding Rh-positive children in the family, they were able to deduce that protection developed at the earlier pregnancy—that is, in their terms, the sensitising as opposed to the immunising pregnancy. They had previously described how an adventitious factor other than ABO compatibility must also operate and now argued that this too must have its effect at the sensitising stage. Their latest paper [13] describes a retrospective analysis of pregnancies known to have led to sensitisation and a comparison of these with matched controls. They found in the sensitising pregnancy an increased incidence of toxæmia, placental

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2. Walker, W. *Brit. med. Bull.* 1959, **15**, 123.
3. *Lancet*, 1959, ii, 549.
4. Hattersley, P. G. *J. Lab. clin. Med.* 1947, **32**, 423.
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10. Mourant, A. E. *Nature, Lond.* 1947, **160**, 353.
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14. Finn, R., Clarke, C. A., Donohoe, W. T. A., McConnell, R. B., Sheppard, P. M., Lehane, D., Kulke, W. *Brit. med. J.* May 27, 1961, p. 1486.
15. Knox, E. G., Walker, W. *Brit. J. prev. soc. Med.* 1957, **11**, 126.
16. Nevanlinna, H. R. *Ann. Med. exp. Fenn*, 1953, **31**, suppl. 2.
17. Levine, P. *J. Hered.* 1943, **34**, 71.
18. Levine, P. *Arch. Path.* 1944, **37**, 83.
19. Knox, G., Murray, S., Walker, W. *Brit. J. prev. soc. Med.* 1960, **14**, 77.

abnormalities, and surgical procedures which could disturb the placental site and facilitate the passage of fœtal blood into the mother. This they claim is their " adventitious factor ". Certainly their work indicates that any steps to prevent immunisation must be taken at the sensitising stage; for once sensitisation has occurred immunisation follows automatically with any subsequent Rh-positive pregnancy. A similar conclusion was reached by NEVANLINNA and VAINIO [20] after they had observed that compatibility between mother and child in affected families was commoner with healthy than with affected children.

The other series of studies, made in Liverpool, is based on hæmatological rather than epidemiological techniques. FINN et al.[14] applied differential elution of adult and fœtal hæmoglobin by means of citric-phosphate buffer on blood-smears of 256 women (mainly Rh-negative) shortly after delivery, and demonstrated a significant number of fœtal cells in the maternal circulation in 12% of cases. Of the 30 women in whom significant numbers of fœtal cells were detected, the amount of fœtal blood in the maternal circulation was estimated to be 5 ml. or more in only 4; in the majority the amount was less than 1 ml. None of the women in whom fœtal cells were detected had ABO heterospecific fœtus; and this they claim confirms the supposed mechanism of protection—namely, that ABO-incompatible cells are very rapidly eliminated and thus do not act as an effective Rh antigen. They subsequently followed up 85 Rh-negative women of this group who had had Rh-positive infants; in many of these women they had detected fœtal red cells. In 3 antibodies developed within three months of delivery, and 2 of these were from the group of 3 women in whom the estimated fœtal transfusion was more than 4 ml. Finally, they injected 5 ml. of compatible Rh-positive blood labelled with ^{51}Cr into each of 6 Rh-negative male volunteers. Thirty minutes later they injected 10 ml. of anti-D serum, with a titre in saline and albumin of 1 in 64, into 3 of these, the others serving as controls. Whereas the Rh-positive cells survived normally in the controls, about 60% were eliminated within the first few hours by those who had received anti-D serum. By means of a modified mixed agglutination technique they studied the fate of the Rh-positive cells not so eliminated and showed that many, if not all, of these cells were coated with anti-D serum and were therefore possibly incapable of stimulating antibody formation.[21] None of the men who were given Rh-positive cells developed antibodies during the period of the study, so it is impossible to say whether the anti-D serum did in fact give any protection.

In the Newcastle investigation the frequency and timing of hæmolytic disease led to the conclusion that the sensitising pregnancy was the important one, and certain obstetric conditions in this pregnancy were found to be associated with sensitisation. The Liverpool investigation revealed the presence of fœtal red cells in women shortly after delivery, and some correlation between the size of such " transfusion " and the risk of immunisation. Both groups of workers emphasise that any preventive steps must be taken at the sensitising pregnancy and consider whether an artificial substitute can be provided for ABO heterospecificity. This may not be feasible by simply administering anti-D serum to " at-risk " mothers—although there is no risk to the fœtus if this is administered only after delivery. Hæmolysed erythrocytes phagocytosed by the reticulo-endothelial system may stimulate antibody production,[22] for we know that heterospecific pregnancy and ABO-incompatible transfusion often cause a rise in titre of anti-A or anti-B agglutinins or the development of immune antibody.[23] An immune response may also occur to a group-specific substance other than that in red cells—for example, when a heterospecific fœtus is a " secretor " [24] or after the injection of T.A.B. or tetanus toxoid.[25]

Much further work will have to be done before Rh hæmolytic disease can be prevented. Meanwhile obstetricians would do well to remember that the first or any subsequent Rh-positive fœtus of an Rh-negative woman may initiate immunisation, and that procedures liable to upset the integrity of the placental site should if possible be avoided. The need for such caution is emphasised by the report by Dr. APLEY and his colleagues, which appears on an earlier page of this issue, of a case in which severe fœtal hæmorrhage into the maternal circulation was probably caused by the use of a Drew-Smythe catheter to rupture the hindwaters.

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Annotations

NON-SPECIFIC SEROLOGICAL TESTS FOR SYPHILIS

UNTIL recent years the tests for the serological diagnosis of syphilis were apparently non-specific in the immunological sense, in that crude tissue extracts and later purified phospholipids, such as cardiolipin, were used as antigens. Nevertheless the standardised complement-fixation and flocculation tests were highly sensitive, and were thought to give few non-specific reactions except in some well-recognised conditions such as leprosy and malaria. In 1949 Nelson and Mayer [26] introduced the treponemal immobilisation (T.P.I.) test, in which a living strain of virulent *T. pallidum* is used as antigen. This has proved a sensitive and specific index of treponemal disease; but as yet no serological test will distinguish between the individual treponematoses.

The most important use of the T.P.I. test has been for verification in patients with no clinical evidence of treponemal disease but whose sera have given positive reactions with lipoidal antigen tests (S.T.S.), the diagnosis lying between a latent infection and a non-specific S.T.S. reaction. Such reactions may be " acute " or " chronic ". The term " acute " is applied to a transient reaction lasting a few weeks or months; and in such cases a precipitating cause, such as recent vaccination or upper-respiratory-

tract infection, may be apparent. This reaction may only reflect abnormally labile individual reactivity to stimuli which do not affect the majority of people. Some women, for instance, have positive reactions in successive pregnancies, becoming seronegative after each delivery. This type of reaction is not at present thought to be important.

The chronic " biological false positive " (B.F.P.) type of reaction, which is arbitrarily defined as lasting more than six months, has attracted more attention. Moore and Lutz [27] investigated 148 white patients who had been observed in private practice for an average period of six years and who were assessed as chronic B.F.P. reactors. Two-thirds of these patients had regarded themselves as in perfect health when the S.T.S. (which in most cases were performed as a routine procedure) had originally been found to be positive; the other third had only minor complaints. On investigation, systemic lupus erythematosus was found in 10 cases, probable collagen vascular disease in 45, and rheumatoid arthritis in 7; an additional 5 patients had undiagnosed serious illnesses. In the clinically healthy group, 43 patients had abnormalities of their serum-proteins—usually of the γ-globulins. Similar studies by Miller et al.[28–30] in New York have confirmed Moore's original findings. Catterall [31] reported an investigation of patients attending the London Hospital who were found to have positive S.T.S. but no clinical evidence of syphilis and whose T.P.I. tests were repeatedly negative. Under very stringent diagnostic criteria, 36 women and 18 men were accepted as showing chronic B.F.P. reactions. In 6 of the women systemic lupus erythematosus developed while they were under observation, and 1 died of this disease; 1 had discoid lupus erythematosus with severe hypochromic anæmia and abnormal liver-function tests; 2 had a rheumatoid type of arthritis; 2 had Raynaud's phenomenon; and 1 had an acquired hæmolytic anæmia. Only 8 out of the 36 women showed no clinical or laboratory evidence of disease apart from the B.F.P. reaction. The findings among the 18 men were less severe: 1 patient died of polyarteritis nodosa; 2 had discoid lupus erythematosus (1 of these also had severe peripheral vascular disease); 2 had rheumatoid arthritis; and 1 had hæmolytic anæmia. In 8 of the male patients the B.F.P. reaction was the sole abnormality. 11 of the 54 patients investigated had a history of sensitivity to penicillin, and 4 of them had had very severe reactions after its administration. In at least 2 of the cases the onset of symptoms could be dated from the giving of penicillin by injection.

It is now firmly established that the chronic type of B.F.P. reaction may be associated with disease, which is often serious. It is also clear that the reactions may at first be unassociated with other abnormalities but that these may follow after quite a long interval; in cases reported by Haserick and Long [32] several years elapsed between the discovery of the B.F.P. reaction and the onset of lupus erythematosus. These reactions should not be regarded lightly: their discovery should be followed by a thorough investigation to detect the conditions commonly associated with them. If no underlying disease is found, it is a wise precaution to keep the patient under observation. In such cases treatment with penicillin is best avoided in view of the risk of inducing sensitisation reactions or precipitating manifestations of disease.

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31. Catterall, R. D. *Quart. J. Med.* 1961, **30**, 41.
32. Haserick, J. R., Long, R. *Ann. intern. Med.* 1952, **37**, 559.

There is little information about the prevalence of either the acute or the chronic type of non-specific S.T.S. reaction in routine serological tests for syphilis. Wilkinson and Sequeira [33] found that the sera of 27·5% of 244 pregnant women and of 35% of 69 blood donors whose S.T.S. had been found positive had a negative T.P.I. test, suggesting that the S.T.S. reactions might be non-specific. A very similar prevalence—26·1% T.P.I.-negative sera among 176 white antenatal patients with positive S.T.S.—was found in a study carried out by the British Cooperative Clinical group.[34] Both these investigations were based on examination of selected sera, but they do suggest that non-specific reactions are not rare.

If the sensitivity and specificity of the S.T.S. in use in hospital laboratories remain constant, the diminished prevalence of syphilis in the general population should result in a greater proportion of the positive reactions found on routine testing falling into the non-specific group. Miller [29] has reported such a rise among unselected clinic patients in New York: in 1950–51, 24·4% of positive S.T.S. were non-specific, judged by the T.P.I. test; in 1956–57 the figure had risen to 43·0%. While the total prevalence of syphilis has fallen, it must be remembered that both in this and in other countries the number of cases of early infectious syphilis has increased in the past two years. Although the numbers are still small in comparison with those in the late war, the increase is disturbing evidence that syphilis is not a disease of the past. This emphasises the need for continuing routine serological testing on as wide a scale as possible, as a means of locating unsuspected cases. The standard S.T.S. are reliable screening procedures for this purpose, provided that the possibility of non-specific reactions is borne in mind, and that, when necessary, recourse is made to the specific tests using treponemal antigens.

CEREBROSPINAL FLUID AS A SPACE-OCCUPYING LESION

WHEN a unilateral space-occupying lesion in the supratentorial cranium has caused tentorial herniation, removal of the tumour may not cure the condition. The brain is swollen, the pressure remains high, and the herniation persists. The medial portion of the temporal lobe—particularly the uncus of the hippocampus—is displaced downwards between the edge of the tentorium and the cerebral peduncle. The third nerve is compressed and stretched,[35] the posterior cerebral artery is occluded, and small vessels supplying the brain-stem are distorted.[36] The classical signs are ipsilateral oculomotor palsy and contralateral spastic hemiparesis, followed by coma with automatic respiration and bronchial hypersecretion. The brain-stem is displaced to the other side and may be forced against the opposite tentorial edge and grooved (Kernohan's notch),[37] resulting in quadriplegia from the superimposition of ipsilateral spastic hemiparesis.

After removal of a tumour one of several procedures may be followed in order to reduce the herniation—subtemporal decompression, intrathecal insertion of saline, or elevation of the temporal lobe by open operation. Ford and Spatz [38] observed dilatation of the opposite lateral ventricle and of the third ventricle associated with

33. Wilkinson, A. E., Sequeira, P. J. L. *Brit. J. vener. Dis.* 1955, **31**, 143.
34. *ibid.* 1959, **35**, 162. See *Lancet*, 1960, i, 740.
35. Reid, W. L., Cone, W. V. *J. Amer. med. Ass.* 1939, **112**, 2030.
36. Scheinker, I. M. Neurosurgical Pathology. Springfield, Ill. 1948.
37. Kernohan, J. W., Woltman, H. W. *Arch. Neurol. Psychiat.* 1929, **21**, 274.
38. Ford, R., Spatz, E. L. *New Engl. J. Med.* 1960, **263**, 263.

a unilateral expanding mass, and suggested that the cause was obstruction of the aqueduct from distortion. They recommended drainage of the opposite ventricle by an indwelling catheter, which they left in place for seventy-two hours. The scalp was cleaned daily with hexachlorophane; and, even without antibiotics, infection did not occur. In such cases ventriculography does not often show dilatation of the third ventricle, but dilatation of the opposite lateral ventricle certainly is common. Often a block of the contralateral foramen of Monro can be shown by pneumoventriculography.

Shrinking of the brain by intravenous urea is another method of reducing swelling and unblocking the obstruction; but it is important to have more than one method for countering the condition, which otherwise goes on to irrversible coma and death. Quite often—notably in subdural hæmatoma—persistent tentorial herniation is not accompanied by a high pressure. Dehydration or drainage is then inappropriate; and nursing with head lowered, and intrathecal instillation of isotonic saline solution, in order to reduce the herniation, are of value.

INDUSTRIAL BLADDER TUMOURS

WHEN, in 1894, it was first recognised that bladder tumours in men could develop after exposure to industrial chemicals, the unfortunate term "aniline-dye tumours" was applied to such cases. It is extremely doubtful whether aniline as such has ever produced a bladder tumour. The tumours were produced by exposure, in the process of dye manufacture, to the dye intermediates—mainly β-naphthylamine and benzidine. Both these substances were used subsequently in various industries before it was realised that they and their associated compounds were carcinogenic. Part of the delay was due to the long latent period between exposure to the chemical and the development of the bladder tumour; on average this is seventeen years, but it may be as long as forty years. Even now clinicians may fail to recognise the industrial background in such cases. Recently two patients with bladder tumours were seen by an astute clinician who, finding that both these men were working in the same part of a chemical factory, contacted the factor and discovered that each had been handling an analogue of benzidine. When this information was appreciated by the company, the process was stopped immediately.

In order to assist doctors who may come across cases of bladder tumour of industrial origin, the British Association of Urological Surgeons has, with the assistance of the Inspector of Factories, the British Rubber Manufacturing Employers Association, the British Chemical Manufacturers, and the Ministry of Pensions, produced a report outlining the possible risks and the occupations and industries where such risks may be encountered.[1] Since 1952 the recognised carcinogenic substances have no longer been used, or their use has been restricted, or they have been modified. The manufacture of α-naphthylamine was stopped in 1952. Benzidine base was also restricted about this time; but the chloride and sulphate salts of benzidine are apparently still available. Xenylamine (4-amino-diphenyl) was never manufactured in this country, although limited amounts were imported. This substance caused an epidemic of bladder tumours among workmen in the U.S.A. in 1955, when over 11% of the men in one factory were found to have tumours. Xenylamine has now been modified by the addition of an organic group which is reputed to render it non-carcinogenic.

In Britain, though the recognised risks have been largely eliminated, owing to the long latent period cases clearly due to industrial exposure will continue to be seen for many years; and possibly cases may be found to have arisen from industrial processes where the risk has not yet been recognised. Most of the intermediate substances were manufactured in the dyestuff branch of the chemical industry; but, with the exception of auramine and magenta, the finished dyes are innocuous. In the textile industry intermediates—benzidine and α-naphthylamine are applied to the cloth and then developed into an insoluble dyestuff. In the rubber industry the intermediates were used by some firms as an antioxidant to harden the rubber. This immense industry includes the manufacture of tyres and tubes, adhesives, rubber-belting, proofed fabrics, clothing, flooring, surgical rubber goods, sports goods and toys, latex and plastic foam, ebonite, and rubber footwear. Of the other industries, factories making certain types of electrical cables, factories where paper is specially processed, and laboratories where benzidine or orthotolidine were used are all possible sources of industrial bladder tumours.

Industrial bladder tumours are reported in 50–60 cases per year out of a total mortality from this cause of about 2000, but the incidence of bladder tumours is increasing in the younger male age-groups, and every effort must be made to identify now and to stop the use of any substance that in years to come will result in the development of bladder tumours.

1. *Brit. J. Urol.* 1961, **33**, 1.

MUMPS 1961

THE present epidemic of mumps appears to be nation-wide—a good opportunity for making detailed observations on this interesting disease. It would be a mistake to imagine that there is nothing to be added to our understanding of mumps, and much-needed information can be acquired with no more equipment than a general practice of reasonable size, an honest and experienced clinical eye, and some hard work.

In the current outbreak an unusual prevalence of some of the less common complications has been reported from several areas. Some patients, during the subsidence of the sialadenitis, which may have been mild, develop "gastroenteritis" with vomiting, abdominal pain, and diarrhœa. The symptoms may drag on for a week or more, and no bacillary pathogen can be isolated from stool or vomit. These patients may have pancreatitis due to the mumps virus, and they merit careful attention. A number of inquiries suggest themselves. It would, for example, be of interest to know the general incidence of the syndrome, the specific attack-rates by age and sex, and the proportion of mumps sufferers in whom this complication develops. It would be even more rewarding, from such a statistical baseline, to follow the later history of the patients in case they carry an increased liability to pancreatitis or diabetes.

How much of the present outbreak of "gastro-enteritis" is mumps in which the salivary glands have escaped whereas the pancreas has not? Again, it has been said that in the infant the salivary swelling of mumps is replaced by lymphadenitis in the neck. Only the virologist and the clinician working together can establish or disprove this remarkable claim. Unfortunately the virological side

of the partnership faces as many difficulties as the clinical, and antigens common to a number of different viruses make the serological picture very perplexing. Nevertheless the investigations ought to be attempted.

Cases of meningoencephalitis are being reported, and here too the incidence ought to be precisely determined. It seems that the organ affinities of the mumps virus may vary from outbreak to outbreak. It is a pity to be uncertain about these matters when accurate recording and analysis might transform speculation into knowledge.

SALMONELLA INFECTIONS

THE genus *Salmonella* first came to the notice of bacteriologists as the cause of outbreaks of diarrhœa and vomiting affecting many people who had had a share in some communal feast. (It is still true that funerals, weddings, and municipal junketings seem to offer especial risks of such infections.) But as bacteriologists became more numerous and more skilful it became clear that isolated salmonella infections are far commoner than those acquired at a common table. The latest return from England and Wales showed that for every large outbreak there were about fifty isolated or familial infections.[1] The origin of these isolated infections can seldom be traced, but a paper by Harvey and Powell Phillips [2] suggests that they are not so mysterious as they had seemed.

The Moore swab has become an accepted weapon of the epidemiologist in search of salmonellæ, and in this inquiry these swabs were placed at weekly intervals in the drains from a large bakehouse and from the lavatory used by the bakehouse staff. We have no doubt that the investigators were at once pleased and shocked by the results, for 31/111 swabs from the bakehouse and 15/93 from the lavatory were positive. Except for the presence on two occasions of *S. paratyphi B* the serotypes found do not call for comment, and further studies made it fairly certain that all these organisms reached the bakery in the raw materials and not on the hands or in the bowels of the staff. In a period of five years only two outbreaks of food-poisoning in Glamorgan could be reasonably blamed on the products of any bakery. One of these followed a school Christmas party—merrymaking was once again to blame—and of about 280 adults and children exposed to risk 209 were infected and some were very ill indeed.[3] Suspicion fell on a trifle, and from the fragments which remained both *S. typhimurium* and *S. thompson* were isolated. 117 victims harboured the first, 23 the second, and 69 had both. *S. typhimurium* of the same phage-type was found in 4 members of the staff of the bakery where the trifle had been made and from the bakehouse drain. Some further evidence suggested that both organisms had been derived from eggs. The compounding of trifle requires extensive manipulation, but the exact process by which it became infected remains unknown.

Moor swabs were also set in the drains from abattoirs: 111/274 yielded salmonellæ of 21 serotypes. Since they were first published the annual returns of food-poisoning have shown that meat products are the most important source of food-poisoning in this country. Despite an elaborate system of meat inspection quite a lot of carcass meat, both home-killed and imported, harbours salmonellæ.[4] The chief interest in these observations from Cardiff lies in the close association in time between the emergence of a (locally) new phage-type of *S. typhimurium* in the abattoir drain and its appearance as the cause of disease in man in the same district. Perhaps of even greater importance was the simultaneous recognition of the same phage-type as a cause of disease in farm animals in South Wales.

We may well ask how it is that the entire population of Glamorganshire does not suffer from repeated salmonella infections. Few of them eat their meat and eggs raw, but experience suggests many ways in which salmonellæ in the bakery or abattoir could reach the table. But there is evidence that farm animals can consume large quantities of feeding-stuffs contaminated with salmonellæ without showing any signs of disease beyond the transient excretion of the organisms in the fæces [5]: and the same is probably true of man. Disease results when some other factor besides host and parasite enters the equation. Resistance to infection is relative and inconstant, and depends on many factors about which little is known. It may be simpler to assume (until we know better) that the dose of salmonellæ swallowed is critical. The infection of large numbers of people is often due to salmonellæ in some vehicle (such as milk which has not been cooled) which encourages almost unlimited multiplication. The infected trifle may have offered similar opportunities for increase, and an estimate of the numbers of organisms would have been interesting. We now know enough about salmonella infections to suggest that the time is ripe for quantitative methods.

ASSESSMENT OF SKIN VIABILITY

IN damage to the skin, from whatever cause, the lesion is seldom of uniform depth. In applying the simple modern classification of burns into two categories—burns with partial skin loss and burns with whole skin loss—we should remember that these lesions are often mixed, and deep burns are commonly associated with marginal zones of relatively intact dermis. Much rubbish has been written to the effect that certain methods of local therapy will obviate grafting in most cases: except in burns that are very largely superficial this cannot be true; for skin regenerates only from intact elements in the dermis or by marginal ingrowth of epithelium, which is intolerably slow and involves scar formation.

In most cases of mixed burns, and in some instances of crushing or laceration, accurate assessment is difficult; and assessment is often deferred for some days. This delay is not important where after fifteen to twenty days those areas which are surgically clean but still unhealed are to be grafted; but accurate early assessment is essential where primary excision and grafting are indicated. Jackson and his colleagues [6] in Birmingham, who have investigated this technique thoroughly, believe that it is valuable in selected cases, especially where the areas of deep burning are well defined, and assessment is, therefore, relatively easy.

Occasionally early accurate assessment is impossible by ordinary means. Accordingly Tempest [7] and his colleagues at Chepstow have developed a method of assessment by means of intravenous dyes which stain all viable tissues

1. Food poisoning in England and Wales, 1959. *Mon. Bull. Minist. Hlth Lab. Serv.* 1960, **19**, 224.
2. Harvey, R. W. S., Phillips, W. P. *J. Hyg., Camb.* 1961, **59**, 93.
3. Harvey, R. W. S., Price, T. H., Davis, A. R., Morley-Davies, R. B. *ibid.* p. 105.
4. Hobbs, B. C., Greenwood Wilson, J. *Mon. Bull. Minist. Hlth Lab. Serv.* 1959, **18**, 198.
5. Smith, H. W. *J. Hyg., Camb.* 1960, **58**, 381.
6. Jackson, D., Topley, E., Cason, J. S., Lowbury, E. L. J. *Ann. Surg.* 1960, **152**, 167.
7. Tempest, M. N. *Trans. Ass. industr. med. Offrs*, 1961, **11**, 22.

while the appearance of non-viable areas remains unchanged. The dyes which they have tested are ' Disulphine ' (sulphan) blue and kiton fast green. Of the two, the latter is eliminated rather more rapidly—namely, in eighteen to twenty-four hours in adults. (Earlier work of this sort was carried out by Sorsby [8] over twenty years ago in investigations on retinal detachment.) Apart from the patient's abnormal and alarming appearance, and the slight embarrassment that this may cause the anæsthetist from one viewpoint and the relatives from another, there seem to be no serious difficulties. This method should clearly be explored further.

TREATMENT OF CYANIDE POISONING

CYANIDES are deadly poisons. They damage the cytochrome enzyme system by which oxygen is normally transferred from hæmoglobin to the cells. This damage is due to conjugation of the cyanide ion with the respiratory enzyme, ferricytochrome oxidase, which is thereby blocked. Thus all tissues in the body suffer from cytotoxic anoxia, while the blood remains oxygenated and therefore bright red, even in the veins, until respiration fails. In fact low concentrations of cyanide stimulate respiration, causing at first deep gasping inspirations; but this is followed quickly by respiratory failure as more cyanide is absorbed. The progressive cellular anoxia results in very rapid deterioration, with vomiting, convulsions, coma, and often death in an untreated case.

Cyanides are widely used in industry, notably in electroplating, photography, the case hardening of metals, and the extraction of gold from mineral ores. Hydrocyanic acid is used as a fumigant for exterminating all kinds of pests from insects to rats.

Cyanides act extremely rapidly; so treatment is of no avail unless it is applied with extreme urgency. The general treatment of cyanide poisoning includes artificial respiration if breathing is failing, and removal from the environment in prussic-acid-gas inhalation or gastric lavage in poisoning by ingestion. Rest helps to keep the metabolic rate, and therefore the oxygen needs, as low as possible.

Specific therapy consists in administration of a nitrite followed by sodium thiosulphate. The nitrite combines with hæmoglobin to form methæmoglobin, which in turn combines with cyanide ions to form a non-toxic complex, cyanmethæmoglobin. Although the respiratory enzyme has an even greater affinity for cyanide ions than has methæmoglobin, methæmoglobin is in such a relatively high concentration that it effectively competes for cyanide ions and so considerably reduces the blocking of the respiratory enzyme. The cyanide reactions are reversible; hence cyanide dissociates gradually both from cyanmethæmoglobin and from the cytochrome-oxidase-cyanide complex. Cyanide is converted by sodium thiosulphate to sodium thiocyanate in the presence of the enzyme, rhodenase. This method of treatment, which was investigated fully by Chen and Rose,[9] is briefly as follows:

With the utmost urgency amyl-nitrite inhalations are given for about 15 seconds in each minute until sodium nitrite is available for intravenous infusion; 10 ml. of a 3% solution (0·3 g.) is infused fairly rapidly. This is followed by 50 ml. of a 25% solution of sodium thiosulphate (12·5 g.), also intravenously. If necessary these injections are repeated.

Cope [10] suggests that in addition oxygen should be administered. He has shown that the " gasping " respiration which normally follows poisoning with low doses of cyanide does not occur if oxygen is inhaled rather than air, and he believes that this is due to reduction of cyanide toxicity by the raised oxygen tension. He has also shown that in dogs administration of oxygen reduces the electrocardiographic changes which follow experimental cyanide poisoning. Cope cites further experiments which suggest that oxygen therapy reduces the toxicity of cyanide in fish, rabbits, and dogs. He concludes that oxygen exerts a protective effect against cyanide toxicity at the cellular level, and that this property can be used to prevent death of animals from otherwise fatal doses of cyanide. These results, although mainly experimental, seem to justify administration of oxygen as a supplementary measure in all cases of cyanide poisoning.

8. Sorsby, A. *Brit. J. Ophthal.* 1939, **23**, 20.
9. Chen, K. K., Rose, C. L. *J. Amer. med. Ass.* 1952, **149**, 113.
10. Cope, C. *ibid.* 1961, **175**, 1061.

ACADEMIC REWARDS

THE universities of Oxford and Cambridge rely more on prestige than salaries to attract the best teachers. Indeed since February, when the members of the regent house refused to pay medical staff more than non-medical,[1] Cambridge has offered lower medical salaries than any other British university. The Congregation of the University of Oxford has now decided, by 163 votes to 106, to refuse £14,400 a year offered by the University Grants Committee to finance more flexible arrangements within the salary-scale of lecturers and demonstrators, so that the stipends would not be so closely tied to age, though the maximum of any grade would remain the same. To accept this money would have helped to attract academic staff of high quality, but the majority of the members of Congregation considered that to introduce the criterion of market value might create unacceptable inequalities of treatment and arouse the dangers of interdepartmental jealousies and suspicions.

In the discussion it was also pointed out that the amenities and status of university teachers below the rank of professor largely depended on their election to a college fellowship. A fellowship carries a yearly emolument, varying from £150 to £700, and other facilities, such as a college house or lodging allowance, full dining rights, and the status of membership of the governing body of the college. Though medical demonstrators in the preclinical laboratories at Oxford are paid more than their non-medical colleagues, only some are college fellows. A college tends to choose its medical fellow from the departments where its preclinical undergraduates will spend most of their time, and in the clinical school, where the students are no longer undergraduate members, close college ties of this kind seldom exist. The chair of a clinical professor is tied to a fellowship of a specific college, but the university and clinical lecturers may, or may not, be accorded dining rights by a college and are rarely awarded a research fellowship. To open the senior common rooms more widely would create difficulties—from increasing the seating problems in hall to doubling the size of the governing body, but more graduate colleges, such as the newly founded Linacre House, might help. Though the money refused from the University Grants Committee cannot be used for this purpose, it is good news that a committee of hebdomadal council has been considering the whole problem of non-fellows among the teaching body.

1. See *Lancet*, Feb. 11, 1961, p. 328; May 20, 1961, p. 1122.

Points of View

A CRITICAL LOOK AT THE PUBLIC HEALTH SERVICE

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DOCTORS in the public health service tend to be in a chronic state of disgruntlement about their salaries. Though we may have some cause for complaint, we should perhaps remind ourselves that we chose our career with local government in the first place; it was not forced upon us. But I believe justice lies on the side of the public health medical officers, to whom a range of salaries comparable with consultants, senior hospital medical officers, and senior registrars should be awarded. It is not my purpose here, however, to enlarge on that theme but rather to invite attention somewhat nearer home and to inquire whether we have ourselves kept up to date, both in our outlook upon contemporary problems and in the organisation of our service to meet them.

Our professional existence and that of our auxiliaries has arisen in response to a particular challenge. There is no necessary reason for our being*; unless there is a function that we are specially equipped to discharge, we have no right to continuance. Actually, of course, we faced something like this crisis collectively twelve years ago, in the morrow of the National Health Service, when to a good many people the days of the public health service, at least as it had hitherto been administered, seemed to be numbered. Now, in 1961, that threat has retreated and the medical officer of health and his staff hold a position almost as well established as ever—except financially. This is because a challenge to which we are fitted to respond has remained to be met and we have responded to it. For all that, however, our service may have accumulated a good deal of useless wood in different places, which, if pruned, would permit a greater exuberance of flower and fruit. Such a possibility ought to be faced with frankness and determination, without regard to human respect and vested interests.

THE NEW EPIDEMIOLOGY

The reputation of a medical officer of health may stand or fall by his ability to cope with outbreaks of infectious disease. The ultimate test of his manliness (so to speak) is smallpox in his area, with typhoid fever as runner-up. Both these maladies are continuing threats that cannot be despised even today, and the outlines of what may be called the old epidemiology are still clearly seen, extended indeed to include poliomyelitis and other virus diseases in an altogether undefined commitment. All the same, the relative importance of the infectious source of morbidity is immensely less than it was fifty or even thirty years ago, and altogether disproportionate to its place when medical officers of health were first appointed in the middle of the nineteenth century.

Illness of all kinds remains, however, and if, stated crudely, the end of public health is to preserve everyone to die of uncomplicated old age, the challenge confronting us is hardly less than it was a century ago, though the terms of it have changed. Cancer, coronary thrombosis, and accidents are large territories yet to be conquered among killing conditions, and if we adopt the motto of *The Medical Officer*, *Non est vivere, sed valere vita*, as our aim, mental disorders of all kinds, psychosomatic ailments, and chronic rheumatism are to be added. Some argue that these diseases, not being infectious, cannot truly be said to possess an epidemiology; but that surely is a narrow-minded attitude. Every disease arising under definable conditions necessarily has an epidemiology and can theoretically be prevented by modifying the conditions under which it arose. Often enough our idea of the pattern of causes is defective, as it is in the examples named above, but that is true of the infectious illnesses as well. The simplicity of the immediately post-Pasteur epoch has gone the way of the indivisible atom.

The sort of apparatus, administrative and executive, required to meet this enlarged challenge may well be different from what served and still serves the cause of infectious epidemiology. It will obviously depend in the first instance on information, but the techniques of its collection and use still await appropriate development.

MATERNAL AND CHILD WELFARE

A job analysis of the hours spent by professional men and women in the work of a local health authority would show a large proportion of time allocated to maternal and child welfare, taken up at clinics and, for health visitors, by visits to people's homes. Granted that the health visitor has a valuable function (and I am not disputing that), the visit to the home is of the utmost importance. Though the health visitor is now to be regarded as the adviser in matters of health to the family in general, she still needs an acceptable means of entry to be invited across the threshold, and the well-being of a newborn baby is perhaps the best to hand, having value as an end in itself and as a talking-point to other matters. But when that is conceded, it must be allowed that the maternal and child-welfare services as we at present know them grew up in vastly different circumstances from the present ones. Whatever the faults of the Welfare State and however brittle the affluent society, they have at least achieved the best nourished and, materially speaking, the healthiest rising generation in recorded history. Gone are the living scarecrows described by Dickens and Engels, and the worst of the slums where they used to live. Neither by physique nor clothing is the child in Scotland Road or Ladywood easily distinguished from his cousin in Sefton Park or Edgbaston. Can we believe therefore that a system devised to meet and help a vast pool of social subnormality is in correct gear for present conditions? Moreover, in the days when the personal health services began, of which maternal and child welfare is the outstanding example, there was a grave default in the medical assistance available to the populations at risk, a default remedied in theory at least by the National Health Service Act.

It might not be too much to suggest that the antenatal and baby clinics as supplied by local health authorities are now redundant and should be scrapped altogether. Insofar as antenatal clinics meet a need for women who will be confined at home, responsibility for the duties discharged by them should be undertaken by domiciliary midwives and the general practitioners (who have generally undertaken to attend at need as "booked cases"). The role of the health visitor in infant welfare (and for that matter maternal care too) would not be diminished, for she should be attached to the practitioners in her district as their agent for social and preventive medicine

* Philosophically inclined readers will note here the untechnical use of a technical term. The author is aware that there is no "necessary reason" for any being apart from God alone.

with special reference to the young and their mothers. Thus practitioners might be encouraged to hold their own maternal and child-welfare clinics, the health visitor and midwife both being in attendance at the former, the health visitor alone at the latter. A double effect might emerge from a change in organisation of this kind: the acceptance of general practitioners in the role they now claim as their right; and the consequent improvement in quality of the obstetric and pædiatric services they have to offer.

SCHOOL HEALTH

Much the same story can be told of the school health service, of how a scheme well adapted to meet needs of its time has been retained into a very different world. The routine medical inspection would seem to be quite unnecessary among a generation of high average physical health. At the same time, the organisation built to meet the original situation might be satisfactorily adapted to new conditions. While the standard of the many may call for little in the way of health supervision, the defects of the few make it the more necessary, and some system of general surveillance, with special attention to " lame ducks " of all kinds, physical and psychological, seems to be today's answer. Such a change would bring no economy in time spent in schools by doctors and nurses, since to make the work rewarding, a very close and friendly liaison would have to be maintained between parents, teachers, and general practitioners. Both school medical officer and health-visitor/school-nurse would have to know their schools and pupils more closely than at present.

The Ministry of Education is, of course, willing enough to approve the trial of any alternative scheme that can be shown to better current practice. The extraordinary thing is that so little in the way of originality has yet been forthcoming. Has the ingrained habit of traditional usage sterilised creative thought in this direction?

HEALTH VISITOR AND SOCIAL WORKER

There are fashions in welfare usages, as in hair length, hats, and waists. For a long time the health visitor was unchallenged as the angel of the public health service. Today her star is in relative eclipse beside the rising prestige of the social worker whose many-angled versatility has been described if not defined by the Younghusband report. Observers tend to reject the implied conflict and to deny the problem, either by declaring that the respective fields of influence are different or asserting that there is a place for each within the same area. There are, however, some very real questions in this issue that ought to be faced and answered. If the health visitor is not a social worker, how is she to be defined? She certainly does not practise nursing as her colleagues the district nurse and even the midwife practise it. It would be absurd to maintain that in her associations with the families, particularly the problem families of her district, she does not undertake " case-work ", by which arcane commitment she can claim, and must be allowed, recognition as a social worker. But the health visitor claims to be and indeed is primarily a nurse; the generation of health visitor without preliminary nursing training is virtually extinct. Are we to believe, then, that conventional nursing training in the wards of a hospital is the best or an essential foundation for the kind of work she is later called upon to undertake? Patients are still very largely regarded by hospital doctors of all ranks as cases of disease with men and women attached. It might be thought that this was the worst possible education for those whose primary concern is with the human person.

However that may be, there are several positions that health visitors might have been able to capture and have now lost irrevocably, for example, those of mental welfare workers and hospital almoners. Unless they are careful health visitors will also lose geriatrics, to be left very literally " holding the baby " and not much else. They may be largely themselves to blame for this decline of fortune, or it may be their teachers who have failed to read the signs of the times.

THE MEDICAL OFFICER OF HEALTH

There is a tremendous bearing in all this upon the functions of the medical officer of health himself. In the early days of the service, medical officers of health were of necessity recruited from other branches of medicine and represented people whose experience had led them to regard prevention as more valuable than cure and to see in public health the highest expression of their calling. Often they made financial sacrifices for the sake of their vision but they justified their existence a hundredfold, as the increased expectation of life in our day has shown. Naturally they set their assistants to tasks that were then of primary importance, to the saving of lives and the reduction of morbidity among mothers and children. In due course these assistants replaced the pioneers, and more assistants replaced them. So a recognised ladder of promotion was established that served well enough as long as the climbing of the lower rungs was achieved in the presence of live issues. But in our generation we have to ask ourselves whether time spent almost exclusively between conventional maternity and child-welfare clinics and routine medical inspections in school is the best or even a suitable preparation for the post of medical officer of health at a time when originality of thought and a willingness to try out new techniques is more than ever required of the head of the department.

It may be that the answer to the salaries dilemma will arise from this very fact, distressing as it may be to aspirants to top positions who have spent their best years qualifying for them along conventional lines. Since the importance, one might almost say the necessity, of the medical officer of health has been acknowledged by recent legislation, the time must be recognised as ripe to attract new blood and new ideas into the service from other branches of the profession by bringing in those who have been convinced of the value of prevention and have glimpsed new trails to follow by their experience elsewhere; in psychiatry, for instance, or pædiatrics, geriatrics, or industrial medicine. When once the value of this is seen by our legislators, the salary question will be solved automatically, since whatever the value theoretically to be placed upon self-sacrificing idealism, it is not the business of the State to profit from it at the cost of a just wage.

". . . It has been said that interest in disease is negative and interest in health is positive. This emotional use of mathematical terms is to be deplored, but if we are to use them, to me there is nothing more positive than a sick person and nothing more negative than the concept of mental health. I think that the concern of our profession is, and should be, with disease and infirmity—that is to say, with the people who are sick, and not with health, however defined—and I do not think the community has suffered or will suffer by this concentration upon our prime duty."—H. M. SOUTHWOOD, *Med. J. Aust.* May 27, 1961, p. 771.

Conferences

PSYCHIATRY

FROM A CORRESPONDENT

OVER 3000 delegates from almost all parts of the world (but not Communist China) attended the 3rd World Congress of Psychiatry in Montreal on June 4–10 to hear over 450 papers on a great many aspects of contemporary psychiatry. Though the fact that a dozen sections might be meeting at one time made life hard for the obsessional conference-goer of wide interests, and though little new was added to knowledge on this occasion, the balanced programme testified plainly to the breadth of ideas and experiment that can now be reasonably called psychiatric. As Dr. D. EWEN CAMERON (Montreal) said, opening the congress, all progress depended on the mind of man, and though no enterprise demanded more, nowhere did it give more promise than in the attempt to understand man. At one outstanding meeting on scientific creativity the congress was addressed by three Nobel prizewinners.

Science and Ideas

Dr. ALBERT SZENT-GYORGYI (Massachusetts) said that scientific creativity was accessible to study and that genius could be fostered: such people did not appear randomly but in groups of 3 or 4 and his deliberate attempts to bring them to light in pre-war Hungary had shown every sign of success before political changes ended them. In the U.S.A. creative talent suffered by misplaced ideas of democracy whereby the retarded were lifted up at the expense of the outstanding: had half as much money and thought been expended on the very able as on the inferior, leadership would not be so scarce. Quality could never be replaced by quantity, and training more scientists was only part of the answer. In problem solving, he made great use of the unconscious level of thought, and once he started working on a problem, it tortured him until it was solved. The reason for this personal striving lay in the intellectual atmosphere of his early life where creative thought was held to be the only thing worth striving for. Desire to alleviate suffering was, in Dr. Szent-Gyorgyi's view, of small value in research—such a person should be advised to work for a charity. "Research wants egotists, damn egotists, who seek their own pleasure and satisfaction, but find it in solving the puzzles of nature." Material success, however, also played a very small part, and most significant researchers and artists died poor. Mere knowledge did not interest him, it was *new* knowledge he sought, and he often felt ashamed of his general ignorance compared with his colleagues; but really such learning as this would only serve to weigh him down and he preferred to see things without much sophistication.

Lord ADRIAN (Cambridge) pointed out that the most potent factor in promoting discoveries had been the introduction of some new technique. Technical advance was formerly much slower and the young scientist was now faced with abundant facts and theories, copious reference libraries, and the stimulus of past discovery—but he could expect to do much less with known methods than he could with a new instrument or way of analysis giving greater detail. Men capable of forming a new outlook were needed, of course, especially in the physical sciences, but nowadays to look for new facts we needed new tools. So far the modern laboratory was best able to study the physics and chemistry of living systems rather than the organisation of animals and man, but before long, Lord Adrian was sure, we would begin to grasp how memories were stored and relate biochemical systems to particular forms of behaviour. At present we were in urgent need of progress within the social sciences to help regulate individual and community behaviour and discover how human societies may live contentedly together. Advance was bound to be more difficult in social than in physical science, but our increasing research resources must not be used exclusively for fields where the advance was relatively straightforward.

Thinking, according to Dr. LINUS PAULING (California), was much more than solving problems; often it involved the recognition of quite new problems by largely unconscious mechanisms which bore little relation to traditional operations of logic. The creative scientist possessed an innate drive to explore, evident from schooldays, and his discoveries—in mathematics anyway—often had no recognisable application when they were made and were rarely put to use during his lifetime. Dr. Pauling believed there may be a difference between the thinking of the biologist who asked what conclusions one was *forced* to accept from the results, and the physicist who, in similar circumstances, would wonder what ideas there might be, as generally and æsthetically satisfying as possible, that were not eliminated by the results—success in the physical sciences suggested that social science might benefit from this method. There was a need to study how ideas arose and he was convinced that instruction in the art of having ideas was possible though we probably did not know enough yet to plan a course. He favoured the system that required each candidate for a doctor's degree to formulate a dozen new ideas and defend them at his examination: it was possible, he was sure, to train one's unconscious towards this end, for example, by thinking about a problem while waiting for sleep and at intervals during the day—then after a while to let the matter drop. Weeks or months might go by, and suddenly a solution, or part solution, would burst into consciousness. During the interval, he thought, the unconscious had examined and rejected perhaps hundreds of thousands of ideas in relation to the problem before a significant one was spotted and brought to awareness.

Integration and Disintegration

Speaking on child development, Prof. JEAN PIAGET (Geneva) explained that while he had been concerned for many years with the normal development of cognitive functions, the psychiatrist dealt with the disintegration of functions at all levels of development. Since Jackson, the great principle of development had been successive levels of integration, which, in pathological states, broke down in the reverse order—a principle which had been applied by psychoanalysts on the affective level. Piaget's own studies confirmed that in intelligence, as in affect, it was impossible to understand the adult without starting from the child. Time, for example, was a concept usually thought to antedate that of velocity, whereas study of the child showed that the order was almost always reversed—as one may deduce from the theory of relativity. As such observations explained the *integration* process, so would collaboration between psychology and psychiatry help to elucidate *disintegration*.

Description and Theory

Description of the basic phenomena, according to Dr. H. C. RÜMKE (Utrecht), could never be entirely free of theory—there

were many frames of reference within which to assess phenomena, and the greatest danger now threatening psychiatry was to limit one's view to, say, neurological or psychoanalytic interpretations of phenomena. We must distinguish between positive symptoms (rarely, in Dr. Rümke's view, psychogenetically determined) and those negative features in a patient's life, especially in the neuroses and psychopathy, which were not observed immediately. The doctor's subjective feelings about a patient, although misleading and potentially dangerous in therapy, could be of undoubted diagnostic importance in schizophrenia, early dementia, hysteria, and mania. Among countless phenomena (for the understanding of which we owed most to the psychopathology of Jaspers), Dr. Rümke mentioned especially the inward and often manifest timidity of the organically deteriorating person. He suffered quietly in a slow and shrinking world, little equipped to meet the new unknown. Much descriptive work needed to be done to distinguish the normal phenomena of old age from those of arteriosclerosis, general paralysis of the insane, multiple sclerosis, Huntington's chorea, or parkinsonism. Disharmonies seemed to arise in all areas of mental life—fluctuant misconceptions, distrusts, doubts, perversities, criminal tendencies, and a certain kind of humour which at first seemed sharp and original but soon became monotonous. Careful description could also confirm the views of Kraepelin and Bonhoeffer regarding the specificity of exogenous reactions to different kinds of poisons and infections. Dr. Rümke had noted that in his clinic for advanced schizophrenics, affect was much less disturbed than had been held; on the other hand, time-sense was disturbed, the patient becoming partly fixed at the age the disease began. Depression, again, was very different from sorrow due to bereavement, from inferiority feelings, irritation, exhaustion, or apathy. Such differences were important for guiding therapy. Dr. Rumke believed that this "neo-Kraepelinian" approach would integrate much apparently isolated work. A decent description (rare, but they did exist) was more lasting than a fancy theory.

Anxiety

"In the beginning was the Word—and that word," according to Dr. JULES H. MASSERMAN (Chicago), "may well have been Anxiety." Primarily anxiety was due to man's abhorrence of physical injury and death, to his uncertainty about the reliability of his human alliance, and to the thought that perhaps he is, after all, a cosmic triviality. Man tried to combat these in turn by developing science and technology (including medicine), by developing clan, economic, and political compacts, and by trying to encompass the entire universe through his religious and philosophical systems. Treatment of anxiety followed the same predictable pattern—physical and social therapy and indoctrination. Surveying experimental knowledge in each of these three areas, Dr. Masserman pointed to inadequacies in organic, chemical, and constitutional studies of disorder but emphasised recent work that seemed to support inheritance of acquired learning and the influence of conditions during intrauterine life. The consequences of brain damage in animals appeared greater, the earlier in intrauterine life they occurred, but early emotional deprivation made later damage of graver consequence. Early environmental influences on the child were of disputable import, but animal ethology had shown more clearly the importance of factors arising early, or at specific intervals during early life—the "imprinting" of behaviour patterns. Distortion or lack of "information", as in sensory deprivation, gave hints of future understanding of conduct disorders, and, conversely, information overload (in cybernetic terms) had severe effects, even direct brain damage. The phenomenological-existentialist school, however, was subjected to severe criticisms on the grounds of its deliberate vagueness and incomprehensibility. Current therapeutic techniques were also criticised, and Dr. Masserman doubted whether anyone nowadays did any better in the long run than Esquirol's claim (1838) to cure a third of patients and improve a further third.

Psychotherapy

The psychoanalyst who returned to his hospital faced many important challenges (for example, patients' ready transition between neurotic and psychotic phases); and though Dr. LAWRENCE S. KUBIE (Yale) felt that analysis could not solve all the problems of hospital psychiatry, it helped ask a few of the right questions and helped guide training of doctors. Pre-analytic case-conferences gave as little insight as necropsies did before the microscope was invented. Adequate treatment in hospital required a vast staff, and Dr. Kubie wondered whether *intensive* psychological treatment over a short period might not be more fruitful than prolonged admission and spreading the therapeutic butter more thinly, as we do at present. In teaching, the resident should learn something of his own reactions to and impact upon patients, and play-back of random tape-recordings and use of the one-way screen were essential. The acting-out of unresolved conflicts by a therapist may make him very good with patients but ruthless with their families, or vice versa, and the same could be true of hospitals.

One must beware occupational therapy, for a patient may escape terror into activity, as another may fly to inactivity, and the same experience may be either harmful or healing. Relationship between hospital and family needed careful thought, and Dr. Kubie knew of no ideal liaison scheme.

Evaluation and Treatment of "Psychopaths"

Dr. G. K. STÜRÜP (Denmark) said that punishment had often been reduced for offenders who lay in the margin between the clearly sick and the "normal" majority of offenders, but such partially sane people had shown a higher recidivation-rate so that the law had provided for special treatment facilities and for indeterminate sentencing, but only after obtaining a medical opinion from the special institution. 20 years' experience as head of the original hospital at Herstedvester had shown that criteria for admission were: a substantial personality deviation from normal; a considerable risk of new criminality; and a need for special treatment (whether the criminal knew right from wrong was less important). A 10-year follow-up of 1000 patients had shown the personality to be extremely plastic, and Dr. Stürüp denied that psychopaths could not learn from experience: massive deviations, again, were often noted after the criminal act, but settled down after admission. The prisoner usually carried insecurity, fear, and feelings of inferiority behind a haughty or aggressive mask, and almost all privately regretted their criminal conduct. The reactions of conscience, even in the pure psychopath were normal as a rule: such people acted without a normal consciousness of reality although not psychotic in the usual sense. Optimism was especially needed in the staff, for patients often refused intensive treatment for fear of still further failure and disappointment. Chronic offenders (persons punished at least 4 times at short intervals) treated intensively had shown a 44% recidivism over the 5 years after discharge. Property offences had the highest rate (51%), aggressive offenders considerably less (28%), and sex offenders least of all (10%). For ordinary prison treatment of similar cases the rates were respectively 60%, 46%, and 37%. The overall crime-rate rose in the war, but had since fallen steadily and was now near the pre-war rate.

It was hard to draw the dividing line between the psychopath and the "neurotic" offender whose unconscious guilt and desire for punishment made him break the law, and Dr. MELITTA SCHMIDEBERG (New York) criticised the concept of the neurotic crime, which was too vague. Mixed psychopathic and neurotic reactions were frequent. A psychiatrist feeling sympathy for an offender, or finding him responding to therapy, might think that he was not psychopathic. The fact that a patient was arrested was no proof that he really wanted to be: the neurotic who desired punishment had other ways to obtain it, and his conscience would stop him from breaking the law seriously. Fear of punishment, she had

found, was a valuable force in moving the patient to accept treatment. She gave a horrifying account of New York juvenile delinquency with gangs of 75 or more boys, heavily armed and organised on military lines. Juvenile addicts (usually heroin) numbered over 30,000 in the city: law enforcement was inadequate and prognosis with treatment poor. Few seemed to live to an old age. Murderers below the age of 16, almost unknown in other civilisations, were relatively frequent and often came from what appeared good homes. In their child-dominated society, where life was held cheaply, little provocation was needed and the offender showed little remorse. Dr. Schmideberg wondered whether current permissive and non-punitive psychiatric social work may have serious ill-effects.

Explanations in Psychophysiology

Among a number of attempts to correlate mental with physical processes, Dr. GEORGE SIMPSON and Dr. N. S. KLINE (New York) showed that histamine weals were significantly smaller in chronic than in acute schizophrenics, but that acute schizophrenics and other patients reacted normally. Imipramine and prochlorperazine reduced the weal size still further. Dr. E. DUNLOP (Massachusetts) believed that prognosis with various physical treatments and drugs could be predicted by assessment of the autonomic nervous system's reaction (systolic blood-pressure) to certain drugs. Dr. B. L. BUSFIELD (Massachusetts) and others noted that reactive depressives salivated more than endogenously or involutionally depressed people, though a person's feelings of dryness were no guide. There was no correlation between salivation-rate and severity of illness, but depressives with higher rates responded better to treatment.

Trends in Treatment

Reports of work with drugs, though numerous, were proportionately less than has lately been the custom: various phenothiazines came in for closest study but there seemed no great changes in thinking. Dr. J. ANGST (Zurich) said that imipramine did not reduce the incidence of depressive relapse, and Dr. LOTHAR B. KALINOWSKY (New York) preferred electroconvulsion therapy for manic-depressive and involutional melancholia. Leucotomy—rostral or bimedial—retained a definite place, but not in schizophrenia where poor results had unjustly discredited the operation. Though several speakers recommended imipramine for mania, Dr. Kalinowsky pointed out that such drugs could cause the condition.

Psychophysiology

Dr. A. W. MAGOUN (California) traced the origins of the concept of internal inhibition, through Pavlov's work to E.E.G. recognition of delta waves and spindle bursts and the elucidation of the reticular-activating system. Recent studies had shown that excitation and inhibition in this system could be brought about by stimulation in several parts of the brain and the thalamo-cortical system seemed to control in part both gonads and adrenal hormones. Studies after sexual or appetite satisfaction suggested that satiety may simply be the expression of a type of internal inhibition. Dr. Magoun concluded that psychiatry must incorporate this mechanism into its concepts of the inhibition of neural activity, and its understanding of the wellness, as well as the illness, of the mind.

Some Other Subjects

Dr. THEODORE LIDZ (Connecticut) had discovered clear-cut thought disorder in one or both parents of most schizophrenics —a fact which, he said, presented the ætiology in a new light.

Dr. S. F. SEMENOV (Russia) had demonstrated disturbance of kinæsthetic perception in schizophrenics together with disordered motor activity and perception of self and environment.

Dr. F. F. FLACH (New York) and others reported significant reduction of urinary calcium with recovery from depression.

By an oral radioactive-serotonin test, Dr. AARON FELDSTEIN (Massachusetts) and his colleagues showed that imipramine and E.C.T. did not work by the inhibition of monoamine oxidase, but that phenelzine and nialamide probably did.

Dr. THOMAS P. HACKETT and Dr. AVERY D. WEISMAN (Massachusetts) described a number of patients who apparently willed themselves to death during trivial operations. Powers of suggestion or "hexing", well-enough known in primitive communities, seemed to operate even in very civilised ones. The "gypsy's curse" could only be countered with still greater magic.

According to Dr. JUAN LOPEZ-IBOR (Madrid), juvenile delinquency is no problem yet in Spain, where a strong father-dominated family system remains.

Dr. JACK WERBOFF (Michigan) and his coworkers reported that psychotropic drugs given to rats early in pregnancy seemed to cause much higher neonatal mortality, and affected behaviour in the offspring.

Dr. HANS SELYE (Montreal) recorded how purely nervous stimuli could produce fatal myocardial necrosis in specially conditioned animals. Pretreatment with nervous stressors could similarly protect the myocardium from otherwise fatal experimental myopathies.

Dr. DAVID KEY and Prof. MARTIN ROTH (Newcastle upon Tyne) reported that random community inquiry showed that among over 300 over-65s, 25–30% had significant mental disturbance, usually reactive depression or anxiety, yet under 5% were in institutions. Many could be helped by treatment, but they often came too late, after some crisis. Comparing sick and healthy among the aged, those of poor health looked old for their years, had more serious physical ailments, were poorer, less mobile, and had fewer personal contacts. Dr. PETER SAINSBURY (Chichester) noted that the aged living with their children were likely to be admitted to hospital.

Mechanism of Narcosis

Dr. PAULING spoke for the first time in public of his new molecular theory of general anæsthesia. He postulated that narcotic agents (e.g., barbiturates) worked by the capacity of their molecules to form hydrogen bonds with each other, becoming microcrystals. X-ray studies had confirmed the form of these microcrystals and it was evident that the readiness to form H-bonds correlated with the efficacy of the anæsthetic substance. The group of such agents that did not form such bonds, or formed very weak ones (carbon tetrachloride, cyclopropane, chloroform) and the chemically inert narcotics (xenon, nitrogen) could be thought of as "fitting in" to chambers of hydrate microcrystals of varying size but not attached to them. Hydrates of chloroform, nitrous oxide, cyclopropane, and xenon had all been studied. Consciousness and short-term memory might be assumed to consist of electrical oscillations in the brain, lasting for the period in which attention was concentrated on the topic, a reaction which took place in the aqueous phase of the brain (78% of the brain was water) containing ions and protein molecules with ammonium side-chains. Memory, Dr. Pauling thought, related to the laying down of protein. It appeared, too, that the level of these electrical oscillations—of consciousness—depended on the pacemaker in the midbrain reticular activating system, depression of this system producing sleep or narcosis. H-bonded substances might act by interfering with this centre or by increasing the resistances (the impedance) of the brain to upward stimuli. This effect, Dr. Pauling suggested, was due to the microcrystals (mainly water) which entrapped protein side-chains and prevented electrical oscillation. Cooling the brain, which promoted hydrate microcrystal formation, produced deepening coma without a drug. The attraction of, for

example, xenon atoms for each other each in its own hydrate chamber gave extra stability and the electric polarisability of the molecules was the index of their mutual attraction; and this determined the pressure of the gas required to produce anæsthesia.

Views of Russian Psychiatrists

A delegation of 10 psychiatrists from the U.S.S.R., led by Prof. ANDREY SNEZHNEVSKY, attended a press conference on June 7. They said they had been much influenced by the experimental work of Magoun and of Selye, but there seemed no softening towards psychoanalytic ideas, which were firmly stated to be unscientific in theory and method. They commented that papers on this topic were becoming fewer, to the benefit of more useful work in neuropharmacology and electrophysiology. Psychotherapy, however, they used very often, usually with drugs: indeed all disorders, mental and otherwise, should be handled thus, but at a rational and conscious level and related to the material basis of psychiatry that underlies all disorder.

Asked about the mental consequences of rapid change from an agrarian to an industrial economy, the Russians were clear that published statistics showed a lower incidence of neurosis in Russia than in other countries. The new conditions of life, they thought, eliminated many conflicts. Reports of hooliganism and drunkenness connected with the Siberia virgin-lands project were denied: people working there were specially selected, young and healthy. Alcoholism was mostly found in the older generation. The overall morbidity-rates were 5 or 6 clearly mentally ill per 1000, most of whom required hospital treatment, and about 20 cases of neurosis per 1000, almost all of whom were treated as outpatients. Their biggest single problem, as everywhere else, was schizophrenia. Russian mental hospitals had grown up largely by historical accident and were often very large—up to 3000 beds, though most were under 1000.

SURGERY

A LARGE number of Czechoslovak surgeons and others from Great Britain, the United States, the U.S.S.R., East Germany, and Yugoslavia met in Prague on May 26 for the annual conference of the Institute for Clinical and Experimental Surgery, and the Czechoslovak Medical Society J. E. Purkinje (Section of Surgery).

Resuscitation

Prof. B. ŠPAČEK (Prague) said that a study of the treatment of the irreversible phase of normovolæmic shock had shown that 50% supertransfusion with a balancing of the hæmatocrit was the most effective measure. Of the drugs available, morphine and atropine were promising. The favourable effect of other drugs, described by Wiggers, had not been confirmed; this was perhaps explained by the more strict conditions of hæmorrhagic shock in the present study.

Professor Špaček described two new signs of oligæmic hypotension and of normovolæmic shock: (1) a conspicuous difference in temperatures between the snout and the rectum, and (2) a simultaneous occurrence of constrictive and vasoparetic changes in the fine vessels of the gum margin.

Dr. P. MÁLEK (Prague) in using the fluorescence of tetracycline analogues under ultraviolet light, had shown that the critically shocked animal tolerated intravenous tetracycline badly, and that when death occurred at this early stage the antibiotic accumulated densely in the lungs rather than in its normal sites in the kidney and liver. A similar degree of reduced fluorescence was shown under these conditions after the administration of fluorescein and bengal-red. Increased permeability of the blood-brain barrier was shown by intensive fluorescence of the brain in these animals. In addition to the vital type of concentration of tetracycline, damaged tissues retained it for several days or weeks, and specimens were shown in which experimental cardiac infarction was distinguished by heightened fluorescence at an early stage.

Dr. B. PELEŠKA (Prague) showed a new transistor defibrillator which was portable and could be used with the closed chest. A choked impulse enabled a more physiological type of myocardial stimulation to be applied.

Dr. J. SMETANA (Prague) presented the results of an investigation into the effects of various drugs on the resuscitation of the myocardium in failure from anoxia and hæmorrhage. Systemic arterial and venous pressures and pulmonary-artery pressure were measured. With electrocardiography these measurements showed that noradrenaline was still the drug of choice for tonisation of the feeble myocardium. The appearance of P waves during the period of renewal of cardiac activity was a good sign.

Dr. B. VISLOCKÝ (Prague) showed that in dogs the main effect of staphylococcal toxin on circulation was failure due to reduction of the cardiac output consequent on reduced venous return following stagnation of a large part of the blood-volume in the splanchnic region; the pulmonary resistance increased relatively more than that of the systemic circulation.

Antibiotics

Dr. Málek described studies of tetracycline analogues (T.A.) in bone. Fœtal bones and those of the newborn, and also regenerating adult bone, all showed extremely high concentrations judged by fluorescences in ultraviolet light. Pregnant or lactating animals quickly passed T.A. through the placenta or via the milk to the embryo or newborn. A large single dose of T.A. in the yolk-sac could retard the calcification and shorten the limbs as well as deform them, but in adult animals no unfavourable effect on the regeneration of a bone defect could be demonstrated. While, therefore, the administration of T.A. to pregnant or lactating women should on these grounds be avoided, there was no need to fear interference with regeneration of bone in fractures and grafts in adults.

Dr. M. HATALA (Prague) had studied the effect of intravenous T.A. in white mice, with particular reference to staphylococcal infection. He compared chlortetracycline, which could be shown by ultraviolet light fluorescence to concentrate mainly in the cortex, and oxytetracycline, which showed more in the medulla. Bacterial counts taken at identical times in a series of early-treated and a series of late-treated mice showed that in both groups the bacterial count was smaller after chlortetracycline, but that in late infections, in which microabscesses had already formed in the cortex, the difference between the two antibiotics disappeared within twenty-four hours.

Dr. Z. ONDRÁČEK (Prague) had applied a similar technique to the study of experimental gallbladder infections in dogs. After single doses of T.A. intense fluorescence could be seen in the epithelium. Repeated administration conferred fluorescence on the deeper layers of the wall. These findings were taken as showing that, while the concentration of T.A. from the bile to the epithelium might be important, of greater significance was the access of the antibiotic to the gallbladder wall via its vascular supply.

Transplantation Immunity

Dr. J. VRUBEL (Prague) had studied the rôle of the regional lymphatic system in the development of transplantation immunity. Insufficient attention had been given to the importance of regional and local lymphatic connections in the phases of acceptance and rejection. By means of indirect colour lymphography he had demonstrated an early lymphatic connection of the graft with its bed. Autografts and homografts were connected thus with the host in the second to fourth day. In homografts the connection was lost three or four days before the graft failed. Extirpation of the regional node at the base of the rabbit's ear extended the survival of a skin homograft on that ear from an average of 4·5 days to 19 days.

The second set response could also be abolished in this way. Destruction of the nodes by chemotherapy (nitrogen mustard or radioactive colloidal phosphorus) was similarly effective. Where lymph-nodes immunised against the host were transplanted into the region draining the proposed homograft, grafts might survive for a long time (54–86 days in 12 out of 15 rabbits); in 3 rabbits the survival of such a graft appeared to have been permanent.

Experiment in Surgery

This part of the meeting took the form of a symposium for the foreign visitors.

Prof. IAN AIRD outlined the development of the surgical unit of the Postgraduate Medical School of London in the fifteen years of his directorship. At every stage the clinical work of the surgical department had been steered by developments in the experimental laboratory. The work of the artificial-heart team, now fully established in the treatment of patients, was a good example of this. Much of the present clearing of uncertainty about transplantation of organs and tissues was due to work at Hammersmith on transplanted dogs' kidneys. Some of the unexpected developments in modern pathology were typified by the finding that gastric carcinoma and peptic ulcer were consistently higher in patients of certain blood-groups.

Prof. V. V. KOVANOV (Moscow) showed how in Russia vascular surgery had at last broken with the Carrel tradition, by the development of the mechanical apparatus for vascular anastomosis. Their confidence in this machine was justified by more than 1000 experiments on dogs; the tissues near the stapled anastomosis and the wall of the artery itself were neither of them damaged by the mechanical suture, and showed no reaction to the presence of the tantalum. The method was particularly suitable for infected wounds and for organ transplantation, since there was less damage to the vessel wall than in manual suturing, and therefore less thrombosis.

Prof. A. A. VISHNYEVSKY (Moscow) gave a paper on cybernetics in surgery. Facts established by laboratory research, and the varied circumstances under which observations were made, allowed many possible interpretations; and the use of electronic computers for interpretation was a method of great promise. Certain complex clinical problems—for example, the classification and diagnosis on morphological and physiological grounds of the congenital cardiac abnormalities—might also be interpreted in this way.

Prof. J. VAN PROHASKA (Chicago) outlined the development of our present knowledge of necrotising enterocolitis. Various hypotheses have been put forward including those of adrenal exhaustion, discrepancies in transfused blood, and the effect of therapeutic antibiotics. His own experiments with staphylococcal endotoxin in Chinchilla rabbits had shown that the disease could be induced by extracts of this toxin from patients with the disease, and that death was induced in the Chinchilla when the staphylococcus was able to grow in the gut and produce its endotoxin. Endotoxin alone could produce a non-fatal enterocolitis in cats and kittens, but in man colonies of the organism were always found in the gut in fatal cases.

Mr. H. H. G. EASTCOTT (London) cited the *Concise Oxford English Dictionary*, which says that experiment means a test or trial of something, or a procedure adopted on chance of its succeeding. This meaning of the subject they were discussing allowed him to recall some first attempts: the frozen arterial homograft in 1949, still the material of choice for reconstruction of the limb arteries; the glycerol-frozen corneal grafts of 1954 (only partially successful); and new work which was in hand on protective neutral solutes other than glycerol, which damages the corneal endothelium. He mentioned current work with his colleagues at St. Mary's Hospital, London, on arterial reconstruction for carotid and renal insufficiency. The former series was already large, and results had been good; but they still lacked a method for measuring cerebral blood-flow by which to judge and interpret these clinical results. In renal stenosis however, not only the effect on hypertension, but many more direct measurements of tubular function had been made and much uncertainty thus removed. A most important feature was the recognition of over-concentration of unabsorbable solutes such as diodone, *p*-aminohippurate, creatinine, and inulin. Thus the more densely outlined kidney at pyelography was often the one which was diseased.

Mr. J. R. KENYON (London) outlined his experimental observations on deep hypothermia in dogs. Cooling to 5°C was achieved by means of an extracorporeal pump-oxygenator and heat exchanger of his own design and construction. At this temperature complete circulatory arrest, combined with exsanguination, had been maintained for as long as 45 minutes. After rewarming, metabolic acidosis was usual; but, provided this was adequately controlled by the administration of intravenous alkali, a high proportion of dogs survived for a long time.

Prof. I. POPOVITCH (Belgrade) had, with the help of the Technical Faculty at his university, built three types of pump-oxygenator. In deep hypothermia to an average of 15°C, their results agreed with Mr. Kenyon's. The use of potassium arrest had been abandoned; but cold cardioplegia was well tolerated, particularly in anoxia. The apparatus had been used for experimental valve replacements in dogs; and one type of aortic-valve prosthesis, made in Belgrade, had proved satisfactory in early assessment.

Prof. S. P. PROTOPOPOFF (Moscow) demonstrated examples of the action currents in various experimental preparations, including the intact rabbit diaphragm, and also the pattern of sweat-gland activity and anhidrosis in various clinical conditions. A curious feature was the finding of an area of anhidrosis around acute inflammatory lesions, such as carbuncles, which persisted even after healing had taken place. In leg lesions in several cases an " echo " phenomenon had been observed in the corresponding area of the opposite side. Over varicose veins a sweatless area was often present, but not around a varicose ulcer.

Special Articles

PUBLIC HEALTH LABORATORY SERVICE BOARD

THE Minister of Health has appointed the Board which, under the Public Health Laboratory Service Act, 1960, will take over from the Medical Research Council the administration of the Public Health Laboratory Service. The Act will be brought into force later this year, but the Board is holding preliminary meetings to consider its functions and proceedings. The chairman is Sir Landsborough Thomson, D.SC., a second secretary of the Medical Research Council, and the other members are:

A. H. Clough (formerly under-secretary, the Treasury); Prof. A. W. Downie, M.D., F.R.S. (Liverpool University); Dr. E. Hughes (M.O.H., Reading); Dr. J. Stevenson Logan (M.O.H., Southend); J. R. McGregor (formerly director of finance, War Office); Prof. A. A. Miles, F.R.C.P. (Lister Institute of Preventive Medicine); Dr. P. Alwyn Smith (S.A.M.O., Welsh Hospital Board); Prof. E. T. C. Spooner, M.D. (London School of Hygiene); Charles C. Stevens (I.C.I., vice-chairman, Association of Hospital Management Committees); Prof. C. Stuart-Harris, F.R.C.P. (Sheffield University); Dr. D. Thomson (D.C.M.O., Ministry of Health); Dr. G. I. Watson (College of General Practitioners). The acting secretary is Mr. D. V. T. Fairrie (Medical Research Council).

From July 3 the address of the director and all branches of the headquarters administrative office of the service will be 24, Park Crescent, London, W.1 (MUS 2223).

Medicine and the Law

On Withholding Remuneration

BY OUR LEGAL CORRESPONDENT

REPLYING to Parliamentary questions, the Minister of Health saw no reasons for publishing the names of doctors and dentists " fined " for breach of their terms of service under the N.H.S. But he added that, if the professions concerned represented that names should be published, he would take account of their views.[1]

The Minister's reply raises three questions. Are there grounds for publishing names in at least those cases in which the interests of the public are affected? Is there any justification for the present practice of giving details other than the doctor's name, thus casting suspicion on other doctors in the locality? And is there any merit in the present system of penalties?

The Minister's view, elaborated in his Winchester address to the British Medical Association,[2] is that these penalties are not fines at all but in the nature of damages for breach by the doctor of the terms of his contract with the Minister's agent—the local executive council.

" In the case of the general practitioner this contract is for the ' rendering to his patients of all proper and necessary treatment '. The party who gives the contract is entitled here, as anywhere else, to have it fully and properly performed, or, failing that, not to pay for what has not been performed, and even to be indemnified for gross and inconvenient failure to perform. . . . if the doctor has committed an offence against the law he stands to be prosecuted for it in the ordinary way like anyone else, and nothing in the procedure for breach of contract under the National Health Service protects him; that if the doctor has damnified any person other than the National Health Service he can be sued for damages in a civil action, and again nothing in the procedure just described protects him; that consequently his name and the associated particulars ought no more to be blazoned in public than those of the decorator who agrees to knock £10 off his contract price for painting a house because he admits having made a mess of the ceilings."

This exposition may be considered in the light of four principles:

(1) Because there is no contract between the N.H.S. doctor and patient, the latter cannot always sue if he is damnified by some failure by the doctor to comply with the terms of service.

(2) Failure by a doctor to comply with the terms of service will not in every case damnify the N.H.S.—except perhaps in respect of its public reputation—but the Minister can none the less withhold part of his remuneration.

(3) Damages awarded by a civil court for breach of contract are intended as compensation for the actual loss suffered. In assessing damages, great pains are taken to ascertain the actual loss which the plaintiff has suffered; even where damages cannot be assessed precisely—as for pain and suffering—the principle is compensation for loss.

(4) Unlike the decorator in the Minister's example, the doctor does not *agree* to " knock something off " his remuneration. The medical services committee adjudge him to be in default and, subject to the Minister's review, fix the amount to be withheld. This is more akin to the case where the customer sues the decorator in the courts—and, if that happens, the decorator's name is public knowledge.

These principles suggest that the withholding of remuneration is more in the nature of a fine than damages for breach of contract. For any employer to have the right to withhold remuneration in this manner is so unusual that it can only be justified on the most cogent grounds. It may be argued, however, that such grounds exist in that, first, apart from overprescribing, the great majority of complaints will come from aggrieved patients who have no contract on which they can sue; and, secondly, that the only alternative to a fine is dismissal—a harsh step in view of the fact that medical practice is so largely carried out under the National Health Service.

These two points are not conclusive, however. There seems no reason in principle why the absence of contract between N.H.S. patient and doctor should not be overcome by a statutory provision enabling the aggrieved patient to sue as if there were a contract. In that case, damages would be awarded to the patient on the basis of the proved loss to him. If this were done in the ordinary courts, the question of whether or not to publish the doctor's name would not arise—as in every other civil action the matter would be left to the Press.

If this procedure were adopted, the present system of inquiry by the medical services committee need be invoked only in special cases. If it is considered that the present system should be retained as the standard method of inquiry on the ground that every breach of the terms of service concerns the administration of the N.H.S., there should be some change in the practice of issuing statements to the Press. Either the matter is purely one of internal administration, in which case no statement at all is needed; or it is of public concern, in which case, in fairness to doctors and public alike, full information should be given.

McNaughten Rules in Adultery Cases

A WIFE petitioned for divorce on the ground of the husband's adultery with a woman who intervened in the suit to deny the charge. The husband admitted the adultery charged in the wife's petition. He was a hospital porter at a mental hospital, and the intervener an inpatient at that hospital. The husband had already pleaded guilty at assizes to a charge of having carnal knowledge of the intervener, she being at the material time a female under care and treatment as a person of unsound mind, and had been conditionally discharged for that offence. The answer to the charge of adultery put forward by the Official Solicitor on the intervener's behalf was that at the time sexual intercourse took place between her and the husband she was suffering from a defect of reason due to disease of the mind, so that though she knew what she was doing, she did not know she was doing what was wrong.

The psychiatrist under whose care the intervener was stated that she had been in hospital since July, 1945; in November, 1960, she was reclassified as an informal patient. He said that she suffered from schizophrenia. Until Feb. 17, 1958, she was treated in a closed ward. On that date she was transferred to an open ward and so became able to make full use of the grounds and corridors of the hospital. In May, 1958, she complained of symptoms and was found to be pregnant. At the probable time of conception, her mental condition was such that she would have known that she was in fact in the process of sexual intercourse, but she would have been incapable, by reason of her mental illness, of a full understanding of her actions; she would not have considered whether such conduct was unlawful or morally wrong; she was incapable

1. See *Lancet*, May 20, 1961, p. 1121; and this issue, p. 1400.
2. Powell, J. E. *Brit. med. J.* May 27, 1961, p. 1479. See *Lancet*, May 27, 1961, p. 1162.

of exercising fully those aspects of judgment and understanding of the quality of her acts as a normal person would; she would not have known that promiscuous sexual intercourse was wrong.

Mr. Commissioner LATEY, Q.C., said that he fully accepted the evidence and opinion of the psychiatrist. That evidence brought the intervener within the second limb of the McNaughten rules. The Court of Appeal had decided in recent years that both limbs of those rules applied to the matrimonial offence of cruelty. Counsel for the Official Solicitor had submitted that both limbs of the rules equally applied to adultery. That submission was accepted. It followed that the intervener could not be found guilty of adultery. The wife would therefore be granted a decree *nisi* on the ground that the husband had committed adultery with a woman against whom the charge was not proved.

S. *v.* S. and O. *Probate, Divorce, and Admiralty Division: Mr. Commissioner* Latey, Q.C. June 9, 1961. Counsel and solicitors: Mark Smith (W. H. Matthews & Co., Sutton, Surrey); H. M. Self (J. I. Humphries and Co.); L. I. Stranger-Jones (Official Solicitor); Duncan Ranking (P. Lupton, Law Society).

D. R. ELLISON
Barrister-at-Law.

Registration of Charities

THE Charities Act, 1960, provides for the maintenance by the Charity Commissioners of a register of charities. As from Jan. 1, 1961, new charities (with certain exceptions) must supply particulars for inclusion in the register.

Existing charities are to be registered by stages: on June 22, there came into force an order requiring the registration of charities existing wholly or mainly for the benefit of places in Bedfordshire or Surrey (including Croydon). Orders extending the Act to other parts of the country are to follow in due course.

Registration by the Commissioners is conclusive evidence for nearly all purposes (including relief from income-tax and rates) that an institution is a charity. The Act also empowers local authorities to maintain indexes of local charities, and with the consent of the trustees to review the working of any group of charities. Charities are enabled to work with each other and with local authorities, and the courts are given larger powers to extend the scope of charities whose objects have become obsolete.

The result should be the more efficient working of charitable institutions and the more productive use of the funds of older charities.

Parliament

Naming the Fined

ON the adjournment on June 16 Mr. MARCUS LIPTON asked the Minister of Health for an assurance that the names of doctors and dentists should be published when a local health executive " withheld pay for breach of contract ". He used this official phrase, but he would himself have preferred to describe the procedure as " fining doctors found guilty of neglecting their duty towards their patients ". He submitted that the public interest required that the names should be known. The medical profession was protected by a privileged phalanx, including the Minister of Health, his medical advisory committee, the General Medical Council, the British Medical Association executive, and local health executive councils throughout the country and, in the background the protection societies. During each of the last three years the number of doctors and dentists fined and the amount of the fines had been: 86 doctors and dentists, £3941; 81 doctors and dentists, £3978; 120 doctors and dentists £3914. The number of guilty doctors and dentists appeared to be going up and the average fine, or amount of pay withheld, going down. Was the degree of guilt getting less, or were executive councils getting more lenient? How many of the guilty men appealed to the Minister against decisions of the executive councils, and how often did the Minister increase or reduce the fines; how often did the Minister refer really bad cases to the General Medical Council for further disciplinary action.

As to publishing the names, Mr. Lipton said, the Minister took the view that there was a contract between the practitioner and the executive council to which the patient was not a party. From the point of view of the unfortunate victim of what was euphemistically called a contract, this was a bit specious. In the ordinary case of a breach of contract the aggrieved party was a party to the contract. It would help to hold the scales of justice a little more evenly balanced if the name of the guilty doctor was published, not merely as a deterrent to the guilty doctor, but also for the sake of other patients in the guilty doctor's care, who were entitled to know what kind of person that doctor was. It would also be fairer to other doctors in the neighbourhood who came under a cloud of suspicion whenever a doctor was fined. A doctor in the National Health Service was a public servant, doing a public duty for which he was paid out of public funds. It was not unreasonable to suggest that the public was entitled to know for its own protection who was not doing his job. The Minister said that if a doctor had broken the law, he could be prosecuted. If he had damnified any person, he could be sued for damages. In the general run of cases, these remedies were purely theoretical, especially if one embarked on the expensive and perilous task of claiming damages in a civil court. Mr. Lipton admitted that it might be argued that if the names were published, the penalty might be out of all proportion to the gravity of what the practitioner had done wrong. But in his view, the British public could make a shrewd judgment of what was a serious offence or merely a technical offence. The public could also assess at its true value the genuineness of a spiteful crank or patient making ill-founded allegations. Non-publication was merely a convenient arrangement between the Minister and the medical profession. The *Sunday Pictorial* had lately published two names and had received no threat of legal proceedings. Mr. Lipton suggested that if legal proceedings for publication could have been instituted, the doctor or dentist concerned, with all the special machinery at his disposal, would have slapped in a writ long ago.

Miss EDITH PITT, parliamentary secretary to the Ministry, pointed out that the purpose of the service committee procedure was simply to consider whether a practitioner had complied with his terms of service. It was not to decide between two parties. The courts were available if a complainant sought damages. Nor was it to punish an offence. This was also for the courts. Nor was it to determine whether a practitioner was fit to practise. This was for the General Medical Council or other professional registration body and, in relation to the National Health Service, for the Tribunal. The strongest reason for the non-publication of names was that the service committee procedure was a matter arising out of the contract, and was in addition to, not in substitution for, the patient's right of recourse to the courts, civil and criminal.

The number of cases where remuneration was withheld had tended to diminish in recent years as compared with the early years of the service. Up to the end of 1960, details of 232 cases had been referred by the Minister to the General Medical Council, and 284 cases to the General Dental Council. The number of serious cases was small. In 1960, only 370 complaints were investigated by medical service committees throughout England and Wales. In only 87 of these was the doctor found to have failed to carry out his obligations. Of the 87, only 37 were sufficiently serious to warrant a withholding of remuneration. The procedure of reference to the National Health Service Tribunal was available in those few cases where it was thought that the doctor had shown by his behaviour that his continued participation in the general medical service

would be prejudicial to its efficiency. 14 doctors had been referred to the tribunal since the start of the National Health Service; 8 were either excluded from further participation in the service or were allowed to resign on undertaking not to practice under the National Health Service. The names of these doctors were published.

QUESTION TIME

Central Purchase of Drugs

Mr. ROBINSON asked the Minister why he had instructed hospital authorities to discontinue the purchase of all patented drugs from unlicensed sources, in view of the fact that he proposed to invite tenders centrally for only three groups of such drugs. Mr. POWELL: Because it is better that the procedure should be applied centrally. Mr. ROBINSON: Do I take it from that reply that it is the Minister's intention to invite tenders for all the drugs which some hospital authorities have been buying from continental sources in the past? Mr. POWELL: I have not limited my action in advance to the three drugs for which I have asked for tenders, and, whenever I see reason to think that the procedure would be appropriate, I shall consider its application. Mr. ROBINSON: There are other groups of drugs which are being bought now. Is the Minister aware that he has now said that the action taken by individual hospital authorities was perfectly proper and within the terms of the Patents Act? In that case, why has he stopped them purchasing in advance of his taking centralised action himself? Mr. POWELL: In the Government's view, this is the only appropriate way in which drugs could be purchased from unlicensed sources. Whenever it is brought to my attention that there is a case for applying section 46, I shall consider it, without prejudice.

Treatment Charge for Road Casualties

Miss JOAN VICKERS asked the Minister if he would require the regional hospital boards to arrange for notices to be placed in the outpatient departments of hospitals stating the amount that may be charged to casualties under the Road Traffic Act of 1934.—Mr. POWELL replied: The emergency treatment charge is payable by the vehicle user, not by casualties as such. Miss VICKERS: Then why is the actual patient quite often asked to pay 12*s.* 6*d.* before he leaves the hospital?—Mr. POWELL: There is no right to ask anyone but the vehicle-user to pay 12*s.* 6*d.*

Mr. HENRY HYND: Is it not worth while reconsidering this charge, which is made at a very awkward time and is very much resented?—Mr. POWELL: Yes, Sir. In logic, I think that this charge is probably not entirely consistent with legislation since it was first imposed, but it does, of course, involve legislation to alter it.

Prison Medical Service

Mr. ROBINSON asked the Home Secretary what was the present number of full-time medical officers in the prison medical service; what had been the total wastage since 1945 due to normal retirement, death, or ill-health; how many had resigned for other reasons; how many had joined the service in the same period; and how many he estimated were required to implement the policies for penal reform already announced.—Mr. R. A. BUTLER replied: The number of full-time medical officers in the service is 56. Since Jan. 1, 1945, 13 officers have been lost to the service through normal retirement, death, and ill-health; 26 have resigned for other reasons, and 67 have joined. No estimate can be given at this stage of the total number of full-time medical officers who will ultimately be needed to implement the current programme of penal reform.

Tobacco and Taxation

The revenue yielded by the taxation of tobacco products in the twelve months ending on May 31 was £823 million, compared with £801 million in the previous twelve months. This duty is the largest single source of revenue from all the customs and excise duties.

In England Now

A Running Commentary by Peripatetic Correspondents

WHEN Ruskin opened the Bradford Exchange, he said that if there was beauty in the hearts of the citizens it would appear in the beauty of their public buildings. Some such feeling inspired these devoted people who built our Royal Infirmary, a building worthy of the city, of real not artificial stone, to last for generations. I am sure it is the child of many prayers.

This is all changed today. If our fine Infirmary cost extra, in those days it was the affair of the subscribers and injured no-one. But today all the money for the new hospitals must come from the public purse. It will be many a long year before the public purse (so many and heavy are the claims upon it) can adequately tackle this very big task. Therefore hospital buildings should be utility buildings. They need not be ugly, but it is wrong to spend the money on fine and costly buildings—it can only delay the erection of other necessary ones. The only exception, perhaps, that might be permitted is the great traditional hospitals—the show-places for visitors from abroad.

* * *

Dr. Comfort seems to me to have something in his remark last week [1] on the immaturity of many of today's parents. In our suburb most of the mothers are obsessed with the number of invitations secured by, or for, their children. Thus, one mother meeting another will say: "Do you know, Joan is going out every night this month", or "My dear, Jimmy has three invitations for a single evening". The brave few who resist this convention can reply with "How popular Joan must be!" or "Good heavens, my John hasn't three invitations in the whole holidays": which turns the conversation elsewhere, but marks the speaker as a suspect nonconformist. I have a strong feeling that many of the youngsters who are the pawns in this puerile game are uneasily aware that they are being used to offset parental feelings of inadequacy.

* * *

A doctor's life is rarely dull in foreign lands. As the unofficial mayoral adviser I was lately asked by His Worship to have a look at the travelling fair being set up in the municipal park. He said that the main attraction was to be the burial, after hypnosis, of a local man who would lie in the grave for five days.

"An ordinary and rather old bit of showmanship," I remarked, but the Mayor would not accept that. Over thirty years ago, he explained, when a similar side-show was staged, the volunteer had died of suffocation, and his relatives had brought an action for damages against the former mayor and council. Our Mayor was determined no such accident should mar his term of office. After a friendly chat with the showman, an old Coney Island hand, about the tricks of the trade, and an inspection of the equipment and the volunteer, I was able to make a report which satisfied the Mayor.

Our townsfolk are as morbid as people anywhere else. Every afternoon and evening large crowds lined up to gaze in horror through the glass panel at the "corpse" lying peacefully in the grave. On the fifth day a capacity crowd watched a realistic display as the man was brought out of his grave and his hypnotic trance. Fear and relief were the predominant emotions of the crowd when the revived man fought wildly with the four bearers holding him down while he gasped and moaned, "Water, water". Fortunately nobody except me seemed to notice that whereas at his burial the subject had been clad in a white shirt, at his resurrection he wore a blue one.

* * *

She was admitted with an undoubted coronary thrombosis, and told us that for some months she had felt a bad pain in her chest when she took her dog out on the common. We asked if the dog was a big one which struggled. "No," she said, "he's only a little one, but, you see, he has valvular heart disease, so I have to wheel him in a basket."

My dog-loving friends see nothing odd in this story.

1. *Lancet*, June 17, 1961, p. 1335.

Letters to the Editor

WHAT MAKES THE PATIENT BETTER?

SIR,—I greatly enjoyed reading the lucid article by Dr. Meares (June 10). Let me hasten as a physician to assure Dr. Meares that his remarks apply equally forcibly to general medicine and disease of the body as they do to psychiatry and illness of the mind; and let me also congratulate him on expressing his point of view so well without mentioning " transference ", either of the positive or negative variety.

If I understand him correctly, he is saying that recovery from mental illness is often inexplicable in terms of current psychiatric therapy; and he is unwilling to accept the coincidence of a natural remission so frequently following his treatment. Working in a very ordinary sort of hospital, I have had the same experience with physical illness and find that patients often recover for no obvious reason. When I was younger, I thought it was my personality, and that I was one of Dr. Meares' empathists with high intuitive therapeutic grading. I also thought all my teachers had an even higher degree of empathy. Both of these delusions, with a few exceptions with regard to my teachers, I have now lost, forunately for my friends and my patients, because I think this attitude can lead to quackery and overweening pomposity.

In Dr. Meares' case, however, I think he goes to the other extreme and is too modest. I believe that he is probably a good psychologist and can understand people and deal with their troubles, either real or imagined, in an efficient way, so that they realise they have come to the final arbiter when they come to him. I think this shedding of responsibility for illness and symptoms is one of the physician's main therapeutic weapons; and I was surprised that Dr. Meares should think it strange that non-verbal suggestion could be more effective than verbal, although I can understand that many psychiatrists would shudder to think that this is so. I have no doubts that this is so; and I think the hospital atmosphere—the attitude of the staff, both nursing and medical, who accept illness as a matter of course and as a stimulus to do something for the patient—may be therapeutically stronger than any amount of talking.

May I turn aside here to challenge those who are continually complaining that the patient is " never told anything " in hospital? My experience over twenty-five years is that hospital staff usually go to untold lengths to explain such things as illness, the need for surgery, and the plan of treatment to the patients under their care, and I do not think the hospitals I have served are any better than others in this. I think moreover that the staff probably do understand how much a patient needs to know and how much harm can be done to him by too detailed a knowledge of his illness.

I think that admission to hospital is itself to some extent curative. Time is an obvious factor and most illness is phasic. Ill patients tend to last out as long as they can before calling the doctor; and the doctor carries on for a time before asking the hospital's help. In acute illnesses (excluding those threatening life), I have found this brings the patient to the hospital around the second week of his illness—between seven and ten days from the onset. Many acute illnesses begin to improve about this time through the healing power of Nature, and this of course underlines the importance of controls in assessing the value of drugs. Patients with subacute illnesses give a history of from one to three months before admission, and again one is often lucky to be on the spot as the remission begins. Some illnesses have been resistant, in my experience, to the therapeutic effects of hospital admission by itself—asthma, ulcerative colitis, vascular disease, in particular, among many others.

My experience therefore suggests that, in acute and subacute illnesses, unexplained recovery is no more than a matter of timing, admission to hospital coinciding with the beginning of natural recovery. In chronic illness time may again be a factor, though obviously not in every case. In addition the unloading of responsibility on to nurse, sister, or doctor—the almost magical shedding of the burden, possibly reminiscent of " witch doctoring "—may be another reason for hastening natural recovery. Even fear of operation may immediately relieve symptoms, as toothache disappears when visiting a dentist. A third reason for unexplained recovery is the indirect or non-verbal suggestion implicit in the matter-of-fact attitude towards illness of those around the patient, their approach to the patient, and their handling of his problems. Other patients are included, and every ward sister knows the importance of good morale in a ward and how this may vary from week to week.

It is perhaps also pertinent to inquire whether these three causes I have suggested do not play an equally important part in the recovery of some patients for which the credit is given to more orthodox " curative " procedures, including many of the drugs we use. The relative importance of these three causes remains obscure, and, in spite of what I should like to believe, I know from personal experience the truth of the adage: " Blessed is the physician who is called in last."

Ashford Hospital,
Ashford, Middlesex. A. BARHAM CARTER.

SIR,—Dr. Meares has drawn attention to an important but neglected factor in psychiatric treatment, the elucidation of which may be the next step in therapeutic advance. If all such cases could be reported and collected, research into the problem might be possible.

Since such results are often attributed to spontaneous remission, it might be a question of finding the cause of " spontaneous " remission; though often these cases are not followed by the relapse which is not unlikely in cases which remit.

Perhaps it is now time to turn the searchlight of investigation on to the psychiatrist, in the attempt to elucidate this " P-factor " (psychiatrist or personal factor). My impression is that the phenomenon occurs not only in a wide variety of diagnostic categories but also with all personality types among psychiatrists.

Possible lines of research might include detailed case-studies of psychiatrists, especially when these puzzling cures take place. The mental attitude of the psychiatrist towards the patient and in other respects, his state of mind at the time and in relation to the patient; the psychiatrist's background, family situation, &c., may all be relevant to this " P-factor ". In short, the apparatus of clinical research, psychological analysis, and case-study may now need to be switched from the psychiatric patient and concentrated more upon the psychiatrist, the psychiatric nurse, and others having therapeutic dealings with patients.

St. George's Hospital,
Stafford. H. M. FLANAGAN.

EPILEPSY AND CAR-DRIVING

SIR,—Dr. Phemister's article on epilepsy and driving (June 10) confirms a suspicion that there are a large number of people driving who should not be doing so. But his remark " as far as this small study goes, there is no indication that these patients are any more liable to accidents than other people " should be taken with a pinch of salt. His revelation of the epileptic's propensity for making false statements may well account for the small number of accidents reported in his group of patients.

According to the Ministry of Transport, the main contributory cause of road accidents in 1959 was drivers losing control of their vehicles. This accounted for 13,014 of the 102,112 fatal and serious accidents involving motor vehicles (see accompanying table).

Analysis of the Ministry's data shows that the vast majority of those who lost control of their vehicle did so while driving straight ahead. There were in addition, 65,855 accidents in which no contributory action is known. Conceivably some of these were due to epilepsy or transient vasomotor disturbances.

CAUSES OF ROAD ACCIDENTS IN 1959

Cause of accident	Cars, taxis	Mopeds, motor-cycles, motor-scooters	Other vehicles
Lost control of vehicle ..	4708	6803	1503
Excessive speed	3525	3614	1018
Disobeyed traffic sign ..	1088	535	344
Failed to signal movement ..	529	213	308
Did not stop at zebra crossing	434	239	147
Opened door negligently ..	297	..	127
Ill, fatigued, or physically defective	282	124	99
Intoxicated	281	43	78
Crossed solid white line incorrectly	134	107	35
Other contributory action ..	8324	6136	4246
No contributory action, or action unknown	28,976	17,870	19,009

A further interesting fact emerging from these data is that 505 serious accidents were due to illness, fatigue, and physical defect, while only 402 resulted from intoxication. In each group, intoxication is near the bottom of the list of contributory causes. This figure is confined to cases where an arrest was made, or would have been made but for death or serious injury. It does not include all cases in which drinking by drivers has contributed to an accident.

These figures show that the public, the Press, and Parliament have not yet realised the importance of illness in drivers as a cause of serious and fatal road accidents.

Worthing, Sussex. R. H. DAVISON.

SIR,—The paper by Dr. Phemister may lead to a certain sense of complacency about this problem which, in my opinion, is not justified. The giving up of driving by epileptic subjects who have been involved in car accidents can by no means be relied upon. Also it may be extremely difficult for local or legal authorities to discover that a road accident has been caused by a driver having an epileptic attack. Amongst such drivers the following have been observed.

The first was a bus-driver who would stop his bus when the warning of his epileptic attack came, have his minor turn lasting a short time, and then recover and continue on his journey. During a fall he sustained an acute subdural hæmatoma from which he died.

Another driver in his late twenties gave a history of 5 attacks of epilepsy, all of which took place when driving. In the first attack he was driving in the Middle East, whilst with the R.A.F., and for no reason the vehicle was driven off the road and turned over. A year later he did this again, but on this occasion he had two passengers who were able to describe that before he lost control of the vehicle he began to have a fit. He was invalided out of the R.A.F. with epilepsy and as a civilian he had 3 more epileptic attacks, all while he was driving. This case suggests that there may be some epileptics who are particularly prone to attacks while driving.

A third patient who admitted having at least 2 minor attacks when driving, subsequently had a third attack which caused his vehicle to collide with another. Both were badly damaged and the driver of the other car was injured. The patient was found guilty of dangerous driving and allowed himself to be convicted of this offence, without disclosing to the authorities that he had a long history of epilepsy. He knew that as a result of his conviction for dangerous driving he would only lose his licence for a limited period and that then it would be restored. He was able to give me the evidence provided by eye-witnesses which showed conclusively that he was having the early stages of an epileptic attack just before his accident. Although he himself knew that this was due to an ictus, it was not discovered by the court. This man had every intention of continuing his driving when he regained his licence. He went so far as to tell me that I was the only person to whom he had told the real truth of the matter, and that if the authorities became aware of the facts, he would know that there could only be one source of the disclosure.

One patient asked to be certified that he was fit to drive as the police had recently observed him having a fit in his car and deprived him of his driving licence.

In addition to motorists, I have also seen a number of epileptic patients whose illness has caused them to fall in the road or to collide with other vehicles while riding bicycles. Although patients who usually have an aura before an attack may say that they have sufficient time in which to stop their vehicles, it is a matter of common observation that occasionally they may lose consciousness without warning.

I would not regard it as very prudent to accept assurances from epileptic drivers regarding their intentions nor consider them as reliable witnesses in attempting to assess the hazard which they present to other road users, for, according to their own statements, many are quite prepared to sign false declarations in order to obtain driving licences. Are such people to be depended on to speak truthfully when questioned about themselves, if the answers are likely to be detrimental to their own interests? In view of the increasing traffic on the roads the dangers to others caused by epileptic drivers is a matter of very serious concern and I am unable to share Dr. Phemister's equanimity on this subject.

London, N.W.11. J. COLOVER.

SIR,—Dr. Phemister seems to imply that the accident-rate is no higher among epileptics than among normal people. I should like to suggest that this is because the epileptics withheld information when questioned about their accidents.

A year ago last January an epileptic driving a car in the High Street of Oxford had a fit and four other people were involved in the resulting accident. Only one has recovered completely: one has a damaged knee (before, he was a leading athlete of the Oxfordshire police); one has lost the power of speech and is mentally unbalanced because of head injuries; and a medical student is still lying unconscious in hospital.

The driver had had only three previous attacks, and in fact his doctor had given him permission to drive since he had not had an attack for a number of years.

Since patients do not want to believe that any accident they have had was a direct result of a fit, a complete mental blank may develop concerning the happenings immediately before the accident.

Christ Church, Oxford. D. R. BODEY.

SIR,—Anyone who regularly sees a large number of epileptics will agree with Dr. Phemister's two main conclusions: (a) that many of them drive, and (b) that the accident-rate does not seem appreciably higher than among the ordinary drivers.

His article also suggests that the authorities could well afford to be a little more lenient than has been their habit in the past. In particular it would be most helpful if they would reconsider their present policy of refusing a licence to epileptics, however long they have been free of attacks, because they are still taking even a small dose of medicine. If you are ever going to allow a patient to drive again, then surely he is safer with drugs than without, and to place before the patient the choice of giving up treatment and driving, and staying on treatment and not driving is, I suggest, wrong.

Exeter. N. S. ALCOCK.

THE DOCTOR'S LETTER

SIR,—Why should a consultant on grounds of etiquette refuse to see a private patient without a letter from his doctor? Maybe the patient does not wish his N.H.S. doctor to know he is seeking a second opinion; or his doctor may not agree; what then?

The fetish of the "doctor's letter" for fee-paying patients in Harley Street is an inroad into the liberties of the patient in as far as it makes a highly private choice dependent on another's knowledge and consent.

London, E.C.2. G. BLUNT.

TEENAGE MORALS

SIR,—I read with interest the article in your issue of June 17 (p. 1335).

Dr. Comfort refers to the word "teenager" saying "the name itself has been coined to steady the aim of the denouncer". This is surely nonsense since we all know that it was created by those who hope to sell their products to this now affluent age-group. In any case it seems to have lost its normal connotation and to be reaching out so as almost to link with that other unfortunate title "middle-aged".

A further point is his reference to the raising of the school-leaving age. Surely he cannot believe that this is the work of the "professional middle-class". If they possess children who cannot qualify for grammar-school education they will, as far as one knows from experience, make personal sacrifices to send them to paying schools if they consider it desirable. The general raising of the school-leaving age is deplored by any thinking person, and here we agree with Dr. Comfort and the schoolmaster to whom he refers.

In conclusion, my eldest daughter and her friends appear entirely normal, though possibly "square", young people. They receive instruction through school and Church in sexual education and take it all with the required pinch of salt.

Richmond, Surrey. J. E. F. GUERITZ.

CEREBRAL FAT-EMBOLISM SUCCESSFULLY TREATED BY CARBON-DIOXIDE INHALATION

SIR,—We feel that some details of the management of our case reported by Dr. Broom (June 17) should be re-stated and indeed amplified. It is unfortunate that we did not have the opportunity of seeing this communication before publication, since we would have immediately realised that certain errors had occurred, due to the fact that the author's knowledge of the patient was entirely retrospective, and that he might be unaware of many pertinent personal observations.

We should like to state that, firstly, endotracheal intubation was not possible under local anæsthesia, and it was necessary to produce muscular relaxation by succinyl dicholine (20 mg. intravenously) before the larynx could be anæsthetised and the tube passed.

Artificial respiration was then instituted for about one minute after which spontaneous respiration returned, and a mixture of 20% carbon dioxide in oxygen was then administered. The immediate response to this was a marked and increasing tachypnœa, associated with an increase in the minute volume to 30 litres. The fresh-gas flow at this time, and subsequently, naturally had to be maintained at a rate consistent with the minute volume as measured intermittently by a dry-gas meter.

It is incorrect to say that "there was no obvious alteration in pulse, respiration-rate, temperature, blood-pressure . . ." as, of course, there was an initial rise in blood-pressure from the resting level of 125/70 mm. Hg to 210/90 in the first 30 minutes of inhalation, this thereafter falling progressively to 140/80. The respiration-rate increased from a resting level of 30 per min. to a maximum of 46 per min., eventually stabilising at a rate of 25 to 30 per min., with a minute volume of not less than 18 litres. During the period of carbon-dioxide administration an attempt was made to lower the body-temperature, this resulting in a fall of rectal temperature of 3°C in a matter of some four hours. Other observations were, of course, made during this procedure, but we have confined ourselves to the information relevant to the article.

Finally, knowing well the dangers of premature conclusions on inadequate grounds, we should like it to be clearly realised that no special claim is being made on the basis of one case so treated.

Whittington Hospital, London, N.19 A. E. RICHARDSON
W. G. G. LOYN.

EFFECTS OF COD-LIVER OIL

SIR,—I should like to comment on the interesting letters of Dr. Kingsbury (May 6) and of Mr. Tunnicliffe (May 27) in reply to mine of April 29.

I must apologise to Dr. Kingsbury and his colleagues (April 8) if my impression was incorrect, that some association existed between the amount of cod-liver oil administered and the degree of hypocholesterolæmic effect. If however the blood-cholesterol values of the 4 groups of subjects given cod-liver oil are graphed against time, it does seem that the steepest falls in blood-cholesterol were shown by 3 of the subjects (C, D, F) who had received the highest daily doses (50 g.). The observation made by Mr. Tunnicliffe regarding the notable fall in blood-cholesterol when lower doses were employed for a longer time had not escaped me; but in the 3 subjects to whom I have referred, extrapolation of the curves of the fall in blood-cholesterol indicates that this might have been even greater had the highest doses been given for four weeks instead of for only twelve days.

The size of dose for future experimental work in adults does not seem to me to be as important as the amount of cod-liver oil which a parent might think it reasonable to give to his child. I would agree with Mr. Tunnicliffe that adults are unlikely to take more than 2 tablespoonfuls daily. But he must remember that small children do not *take* drugs, but *are given* them. This is, I think, an important distinction; and there is no doubt that many small children *are given*, and retain, surprisingly large amounts of unpalatable drugs.

Mr. Tunnicliffe refers to the opinion of Bicknell and Prescott [1] that 10,000 I.U. is the lowest daily dose of vitamin D_2 which might be considered toxic to children. I do not think that this would now be accepted. Graham,[2] in a review of 38 cases of idiopathic hypercalcæmia, showed that the highest daily dose before the onset of symptoms was 8800 I.U., and that in 8 of his patients the daily intake was less than 1000 I.U. I did not suggest that idiopathic hypercalcæmia in recent years had been caused by vitamin D_3 but this does not mean that it could not do so if it were to be used as extensively as vitamin D_2 has been. I agree that Thatcher's patient [3] seems likely to have suffered from idiopathic hypercalcæmia, but in this instance the source of vitamin D was cod-liver oil, and the daily intake does not appear to have exceeded 1200 I.U.

I would suggest that the correct conclusions to be drawn from Malmberg's experiment [4] with large doses of cod-liver oil given to 2 premature infants are that this substance can cause myocardial atrophy and that this effect may be produced within a few days or weeks. It is an encouraging suggestion that toxic effects such as this may have been attributable to the impurity of the cod-liver oil used at that time, but this I think cannot be regarded as proven.

Mr. Tunnicliffe has referred to the many years of clinical experience in the use of cod-liver oil, but I doubt if we have gained sufficient experience to be sure that the substance is quite harmless. Clinical experience with vitamin D_2 was also extensive, but a decade elapsed after the fortification of infant foods and the institution of

1. Bicknell, F., Prescott, F. The Vitamins in Medicine; p. 840. London, 1953.
2. Graham, S. *Postgrad. Med.* 1959, **25**, 67.
3. Thatcher, L. *Lancet*, 1936, i, 20.
4. Malmberg, N. *Acta pædiat., Stockh.* 1928, **8**, 364.

nation-wide prophylactic therapy before the harmful effect due to relatively small doses was recognised.[5 6] I do not think it an unreasonable suggestion that if, as at present, several hypocholesterolæmic agents are available, those to be used in an attempt to prevent coronary-artery disease should not include any which might conceivably be harmful. It remains to be proved beyond reasonable doubt that cod-liver oil is completely harmless.

Royal Hospital for Sick Children, Glasgow. ERIC N. COLEMAN.

BIOCHEMICAL INDIVIDUALITY

SIR,—Your leading article of March 25 called attention to an important field, but did not do it justice. The whole problem of innate resistance or susceptibility to many metabolic as well as infectious diseases is coming to the fore, and is based upon biochemical individuality (as well as individuality in other fields).

If members of the human family were assembly-line products —all alike—there would be no such thing as innate resistance or susceptibility. My book, *Biochemical Individuality* (1956), is the only one which treats this subjects as well as some related material on anatomical and physiological individuality. The idea of biochemical individuality is crucial to the genetotrophic concept of disease which was first set forth in *The Lancet* in 1950.[7]

Department of Chemistry, University of Texas, Austin, Texas. ROGER J. WILLIAMS.

MEDIASTINAL LYMPHATIC GLAND TUBERCULOSIS IN IMMIGRANTS

SIR,—Like Dr. Silver and Dr. Steel (June 10) we have observed mediastinal lymph-node tuberculosis in coloured immigrants, and also in a young man of Welsh parentage; other cases have been reported from this hospital in both British-born and Asian patients.[8] We would agree, however, that the condition occurs more commonly amongst Indians and West Indians, and that it is associated with low resistance to tuberculosis; in patients with this type of lesion miliary tuberculosis and other extrapulmonary foci sometimes develop. The most immediate danger, however, is rupture of the caseous lymph-node into a main bronchus; and thoracotomy may be urgently indicated.

Most of our patients with this lesion appear to have come from villages or farms in India or one of the smaller West Indian islands. In both cases former generations would have been relatively isolated from infection, with the result that many are still unduly susceptible and infection is rapidly followed by disease. It is because their inherited resistance is poor that their response is inadequate to deal with the primary infection, with resultant massive caseation of lymph-nodes and other severe manifestations of uncontrolled disease.[9]

Many Indian villages, even in the plains, have still little contact with the outside world, and when their inhabitants migrate to a city, be it Bombay, Karachi, or London, many will be meeting infection for the first time. Roe,[10] for example, found in an Indian community at Uxbridge that 29 (66%) out of 44 were Mantoux-negative (1:1000 O.T.); they were mainly Sikhs from farming communities. On the other hand we also find here Indian and Pakistani patients with old-standing cavitary lesions, some of whom arrive in this state.[11] Inevitably, the two groups intermingle, usually under adverse conditions, in the older and more congested parts of our larger cities. The results of this explosive combination are seen in the form of grossly enlarged lymph-nodes, acute pleural effusions, and rapidly progressive pulmonary disease, as described by Stevenson[12] in Bradford.

We would appear to be encountering in this country in small degree what is happening continuously and on a massive scale in India, Pakistan, and other countries where tuberculosis is still rife, and where the progress of industrialisation, with its improved communications and accelerated drift of the rural population to the towns, tends to perpetuate the vicious cycle of infection and disease. Obviously this situation can only be effectively dealt with by extensive and well-planned measures directed towards detecting and treating the infectious patient—and these will take time, effort, and money. Meanwhile, this country could make an indirect contribution by undertaking an intensive study, by X-ray and tuberculin testing, of the Indian and Pakistani communities resident here. A good deal of information is already available; but perhaps this could be coordinated and the methods of effectively controlling the situation more thoroughly elucidated.

Clare Hall Hospital, South Mimms, Barnet. NORMAN MACDONALD
H. L. KHANCHANDANI.

ACTION OF HEPARIN IN ISCHÆMIC HEART-DISEASE

SIR,—In his letter (May 13) Dr. Poller points out that serum has thrombogenic properties by virtue of an antiheparin action or by directly causing thrombosis.[13] He indicates that both the antiheparin activity and thrombus-inducing activity of sera can be removed by absorption with aluminium hydroxide, and that this activity is present in the serum of patients with factor-VII deficiency, severe phenindione-induced deficiencies, and severe Christmas-factor deficiency. Although this activity is decreased in the third condition, it could still be demonstrated.

I think it worth recalling that serum has at least one other property in relation to thrombosis—its power to induce platelet clumping or "viscous metamorphosis" (V.M.) in washed suspensions of platelets. This property was described by Wright and Minot[14]; and I have attempted to define the properties of this platelet-V.M. factor of serum.[15] This factor could be absorbed on to aluminium hydroxide or barium sulphate, and was present in fresh serum derived from blood deficient in antihæmophilic globulin, Christmas factor, factors V and VII, plasma-thromboplastin antecedent, and platelets. In addition it was present in patients who had von Willebrand's syndrome. It was partially destroyed by heat, was stable on storage at room temperature, and required calcium for its action. Heparin neutralised or destroyed the factor completely. It has been claimed that this serum factor is in fact thrombin[16]; but human thrombin will not clump washed suspensions of human platelets, and sera which are capable of inducing platelet clumping cannot convert fibrinogen to fibrin. The factor could be absorbed from serum by washed platelets.

These results do not identify the factor or factors responsible; but they do suggest that Wessler's thrombogenic serum factor might act by producing platelet clumping and so encouraging fibrin formation. It is impossible to connect the platelet-clumping activity with the antiheparin effect, but the association may be of considerable importance.

5. Butler, N. R. *Proc. R. Soc. Med.* 1951, **44**, 296.
6. Lightwood, R. *ibid.* 1952, **45**, 401.
7. Williams, R. J., Beerstecher, E., Berry, L. J. *Lancet*, 1950, i, 287.
8. Harvey-Samuel, R. E. D. *Tubercle*, 1955, **37**, 255.
9. Cummins, L. Primitive Tuberculosis. London, 1959.
10. Roe, J. T. N. *Tubercle*, 1959, **40**, 387.
11. Springett, V. H., Adams, J. C., D'Costa, T. B., Hemming, M. *Brit. J. prev. soc. Med.* 1958, **12**, 135.
12. Stevenson, D. K. *Tubercle*, 1959, **40**, 491.
13. Wessler, S., Reimer, S. M. *J. clin. Invest.* 1960, **39**, 262.
14. Wright, H. J., Minot, G. R. *J. exp. Med.* 1917, **26**, 395.
15. Sharp, A. A. Thesis for the Degree of Doctor of Medicine, Edinburgh University, 1957.
16. Stefanini, M., Silverberg, J. H. *Amer. J. clin. Path.* 1951, **21**, 1030.

Whatever the explanation, these results do suggest that these three activities of serum may be caused by one factor, a factor that is probably distinct from any known coagulation factor.

The Radcliffe Infirmary, Oxford. A. A. SHARP.

RUPTURE OF THE POSTERIOR URETHRA

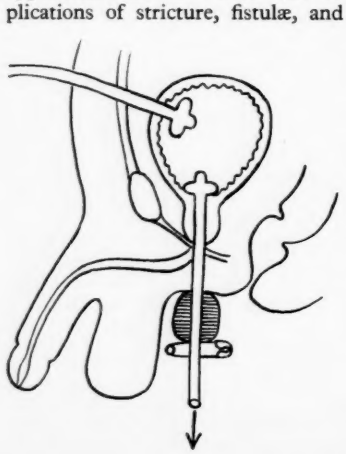
SIR,—I should like to suggest that the fundamental principles of wound treatment, correctly emphasised by Mr. Wilkinson (May 27), are not being fully carried out if the urethral wound is being irritated by urine or by an indwelling catheter, whether a Foley or a plastic one as recommended by Mr. Scorer (June 10). I consider that better—almost ideal—conditions for primary healing are obtained by immediate primary suture, not using a urethral catheter, and nursing in high Trendelenburg posture with suprapubic bladder drainage. By this method the urethra is kept completely dry and non-irritated while healing occurs.

A boy, aged 11, with fracture of the pelvis and complete rupture of the posterior urethra was treated by this method at Willesden General Hospital in 1958; through a perineal incision two hours after injury the wide separation between prostatic and membranous urethræ was overcome quite easily and primary suture performed. The bladder was drained by suprapubic catheter only, and high Trendelenburg posture was strictly maintained for two weeks. The suprapubic catheter was taken out a few days later. Micturition was normal within a few days, and there was only very slight urinary infection. Three years later there are no symptoms. No catheters or dilators have been passed since the initial operation.

I believe that immediate clean primary healing occurred because of the complete absence of irritation of the urethral wound by urine or catheter for two weeks. Unfortunately I have not yet had the opportunity of treating another such case—perhaps owing to the highly organised disposal of such injuries to the proper units!

London, W.1. GEORGE QVIST.

SIR,—Mr. Scorer (June 10) says that the traction method of treatment using a Foley catheter is difficult or impossible to apply to the ruptured urethra in boys owing to the small size of the urethra. He is to be congratulated on the good results he obtained by a non-traction method; but I believe, nevertheless, that traction is the only technique which will certainly maintain the urethral ends in accurate apposition and thus avoid the often irreparable complications of stricture, fistulæ, and incontinence which may be the sequel of simply leaving a catheter across the gap.



Traction is suitable for any age; the accompanying figure illustrates a technique which I used successfully in a boy aged 4½ years. A 14 F de Pezzer catheter was brought through a perineal urethrostomy. The prostate was correctly positioned against the perineal membrane by pulling on the catheter before the bladder and abdominal wounds were closed. Whilst the pull was maintained, adhesive strapping, 1 in. wide, was wrapped around the catheter to produce a firm mass close to the perineal skin; the catheter was transfixed with a safety-pin just below the mass to prevent it slipping. The bladder was drained above the pubis, and a thread attached to the expanded end of the de Pezzer catheter was brought through the wound beside the suprapubic catheter. When the child returned to bed, weight traction was applied to the perineal catheter. This catheter was removed after two weeks, and the suprapubic catheter two weeks later. For three months the child had incomplete control, but he has been fully continent since. Instrumentation has never revealed any narrowing of the urethra; and intravenous pyelography and urinalysis are normal.

A perineal rather than a penile catheter has several advantages. A larger and stronger catheter may be used; there is no risk of stricture formation in the penile urethra; traction can be applied in an axis corresponding to that of the prostatic urethra; and, not least important, it is much more comfortable. The mass of adhesive strapping on the catheter is an essential factor in maintaining the ruptured urethral ends constantly in contact, since they are compressed between it and the expanded end of the catheter. With traction alone there is always the possibility of displacement of the proximal urethra if the pull is temporarily relaxed—as it often is, during movement of the patient in bed.

For my patient I chose a de Pezzer catheter because I was uncertain whether the balloon of a Foley catheter would tolerate traction for a long time. From Mr. Wilkinson's experience it obviously does, and a Foley catheter is probably preferable for the purpose. Incidentally, the smallest Foley catheter obtainable is size 10 F, and not 12 F as suggested by Mr. Scorer.

Alder Hey Children's Hospital, Liverpool, 12. J. H. JOHNSTON.

TREATMENT OF LICHEN PLANUS

SIR,—In your annotation (June 10) you mention 'Dipasic' as a drug which has produced good results in the hands of Dr. Alexander,[1] and say that further trials with this drug are required.

Unfortunately, Dr. Alexander overlooked the natural history of lichen planus. Many cases clear spontaneously in 6–9 months from the time when symptoms begin. Many patients with lichen planus do not see a dermatologist for three months or longer; and if a further three months' "treatment" is added to this, the patient may well reach the period of spontaneous resolution.

If dipasic was of value in treatment it seemed to me to be an important advance; so I immediately tried to reproduce Dr. Alexander's results. In a double-blind trial with dummy tablets, I have had the following results to date after three months' "treatment":

	No change	*Improved*	*Clear*
Dipasic	2	5	3
Control	0	7	6

2 patients given dipasic took the tablets for one month only; as they had not improved they did not return for observation until sent for. After three months 1 had improved and the other was much worse. These 2 are not included in the figures given above.

An additional 12 patients were given dipasic uncontrolled, either because they were seen before I had access to dummy tablets or because they were seen at hospitals where I did not have a supply of dummy tablets. 4 of these patients might be described as difficult because the disease had been present a long time; none of these 4 was improved. The results in the other 8 after three months were:

No change	*Improved*	*Clear*
1	6	1

1. Alexander, J. O'D. *Brit. J. Derm.* 1960, **72**, 355.

In every case where the condition had cleared, the disease had been present six months or more at the time of clearance. From these results it appears that dipasic has little or no influence on the natural progress of lichen planus.

London, W.1. P. D. SAMMAN.

PROFESSIONAL SECRECY AND THE LAW

SIR,—I have felt strongly for years about the powers of courts of law to subpoena doctors to give evidence on professional confidences between the doctor and his patients.

I was recently subpoenæd by a wife to give evidence at a divorce court to substantiate her allegations of cruelty against her husband. Both are patients of mine.

Before giving evidence I told the commissioner that it caused me great distress to have to state in open court facts and opinions based on confidential consultations with the parties concerned. The commissioner replied at some length that, though he sympathised with my point of view, the law as it stood compelled me to give evidence; he himself thought that doctors should enjoy the same privileges as lawyers in this respect, and not be forced to give evidence on professional matters between them and their clients. He also said that if a sufficient number of doctors felt strongly enough about this, the law could be changed.

I should be very interested to know the views of others.

West Hartlepool. M. J. KEATING.

BRONCHODILATORS AND CORTICOSTEROIDS IN ASTHMA

SIR,—I found Dr. Gandevia's letter (May 13) of great interest. He indicates that a few patients with a clinical diagnosis of emphysema and a persistently poor response to bronchodilators will occasionally respond dramatically to steroids. As he points out, these usually have sputum eosinophilia. If they are assumed to have simple emphysema they will not get steroids.

I have previously emphasised the importance of sputum examination in apparent chronic bronchitis and emphysema, and described a speedy and simple method of examining the sputum.[1] This method is so easy and useful that I am surprised that it has not been more widely adopted. I am convinced that it is impossible to distinguish between chronic allergic asthma and chronic bronchitis in any other way. Since then my only modification has been to use a microscope lamp with a flask of water as a lens, the water being tinted with cresyl-blue with a dash of acetic acid to keep it stable. In this light the eosinophils are quite unmistakable.

Dr. Gandevia has also drawn my attention to the work of Dr. Hume and Dr. Rhys Jones.[2] It would have been of interest to know what proportion of patients fall into each of the five groups they described, as, without some idea of the frequency of such patterns of response to 1% isoprenaline aerosol, it is most difficult to judge the importance of their work. Their forthcoming paper may resolve this question.

I strongly deplore the naive tendency to believe that the reading on a machine always takes precedence over the patients' statements, particularly when the estimation of the $F.E.V._{1}$ is assumed to provide an infallible yardstick. Measurement of ventilatory function is only one aspect of respiratory physiology; many other factors must be involved. I have observed that established chronic asthmatics with sputum eosinophilia, when treated with steroids for the first time, sometimes report considerable subjective improvement in their exercise tolerance; but spirometry records either very little improvement or no improvement at all. To my mind two factors are not sufficiently taken into account. Firstly, there can be no doubt whatever but that the $F.E.V._{1}$ is primarily a measure of the power of the muscles of expiration and the degree of rigidity of the thoracic cage itself. It seems probable that a well-established case with a fixed barrel chest may not be able to push out more air in one second whatever the state of the airways. It should, therefore, be possible for the patient's airway to improve greatly but for the $F.E.V._{1}$ to be only slightly increased, because of the rigid thorax. Secondly, in a patient whose $F.E.V._{1}$ is less than 1 litre, very slight improvement may produce subjective improvement which appears out of proportion to the actual increase measured.

I should like to see more interest shown in the gross and microscopic appearances of the sputum. Even simply getting the patient to cough up sputum into a disposable plastic petri dish can provide much useful information. Just as the urologist looks at urine, and the gastro-enterologist at stools, so the chest physician should look at sputum.

The Chest Clinic, Derby. H. MORROW BROWN.

1. Brown, H. M. *Lancet*, 1958, ii, 1245.
2. Hume, K. M., Jones, E. R. *ibid.* 1960, ii, 1319.

THE HANDICAPPED

SIR,—Your leading article of June 10 draws attention to the need for centres for the initial assessment of handicapped children, for periodical reviews of their progress, and to act as an advisory service to the family doctor. You also suggest that there may be a need for a doctor who will make a special study of one type of handicap. Although a few specialised centres would be of great value, I do not think that the need is so much for specialists in each type of handicap as for doctors able to coordinate medical and non-medical services and to mobilise a team composed of members of the services appropriate for each patient.

Many of the problems that beset handicapped people are common to them all, irrespective of age or disability, and stem from ignorance of the available services, from psychological maladjustment, and from adverse social circumstances. By advising patients with any type of handicap, a clinic can gain considerable experience and establish personal contact with many medical, paramedical, and non-medical people. But the doctor in charge should not consider himself a specialist in every medical and surgical condition that the patients may have. He is there to advise and be advised by his colleagues (especially the patient's family doctor), coordinate the efforts of all who are able to help, and give continuity of care. This continuity is particularly important at times of difficulty—such as the failure of the original plan, or the occurrence of a new and unexpected problem—and on leaving school, when a handicapped young person passes out of the supervision of the school medical officer and often of the pædiatrician too.

Royal Free Hospital, London, W.C.1. M. D. WARREN
Chairman, Resettlement Clinic.

SIR,—I visited the diagnostic and evaluation centre at Johns Hopkins Hospital in the summer of 1959 and was struck by the following points in its planning and organisation:

It was set up at the request of the Maryland State Planning Commission and was not started in opposition to the school medical services.

Its object is not merely to make a diagnosis, or diagnoses, but to assess disabilities in terms of the child's present and future educational needs. Many complex learning disorders must be studied in detail, both at the neurological and the psychological level, before a conclusion can be reached which will be of use to the teacher: a diagnosis alone is not enough.

The sole responsibility for the diagnostic programme and for the assessment and follow-up rests with *or* is vested in the director of the centre.

The assessment and special investigations such as audiometry and electroencephalography are, if possible, completed in 2–3 days, so that a coherent impression of the child is gained and frustrating delays are avoided. The centre nurse accompanies the child and his mother to the special departments to ensure that appointments are kept and that parent and child do not get lost and arrive in a state of confused apprehension.

The assessment and projected programme are discussed with the parents before the report is sent out. Copies of the report are sent to the referring physician or organisation, the State Department of Health, the family doctor, and relevant hospital departments.

With the final report a letter is sent to the health department asking for comments on the adequacy and usefulness of the report, and whether the suggested educational programme will be practicable. A second letter is sent later, asking if it has been possible to carry out the recommended programme.

The centre works with the school medical services yet offers an independent opinion. It has the resources of a teaching hospital and facilities for undergraduate and postgraduate study of the educational and social difficulties of the handicapped child, which are probably rare in America and certainly rare in this country. If, as your leader suggests, the education authorities in this country are becoming aware of the changing needs in the school medical service, it would be encouraging to see a similar centre set up in Great Britain.

Teddington, Middlesex. J. A. BLACK.

SIR,—Your leading article (June 10) on the need for team assessment and continued supervision of handicapped children is indeed timely. There is a rapidly increasing number of severely deformed babies for whom special follow-up services and schooling will be required during the next 10 years—those with spina bifida, the group whose multiple disabilities you stress in the second paragraph.

It is unfortunate that your article gives the impression that America has suddenly hit upon the idea of evaluation centres and of development of special facilities for particular handicaps, and it goes on to suggest that such centres might be established in this country. You even go so far as to suggest that an essential member of the team would be an educational psychologist, as though this too were a novelty. It would be a pity if attention were not drawn to the fact that the medical profession in Great Britain has for decades led the world in the care of the handicapped child. Indeed, there is cooperation between hospital and education authorities all over the country. The great pioneers, Robert Jones and Henry Gauvain, should not be forgotten. Today there is at Chailey-Heritage in Sussex just such an assessment centre as you visualise, complete with educational psychologist and all such services. Perhaps one of the greatest obstructions to the further development of this type of centre is the fact that the planning needs to be national and transregional, whereas in the present administration, expenditure and development are related primarily to hospital management committee areas.

You refer to the progress from the deformed infant to the handicapped adolescent in industry; here at the final stage of rehabilitation lies the great weakness of our present welfare state. The provision of hostel accommodation or residential education for the late adolescent and young adult is conspicuous only by its absence, apart from one or two craft-training institutions. It is true that legislation permits suitable children to be retained at school at the expense of the local authority well beyond the normal age for leaving; but with no provision of suitable institutions, legislation is ineffective.

Poliomyelitis and cerebral palsy have attracted charity funds in a large measure in America and many other countries, but the less common and rapidly increasing problem of the incontinent paraplegic is correspondingly less attractive when it comes to public appeals. Deafness and speech defects also perhaps suffer from the counterattraction of public and charity funds to other pressing problems.

Certainly consultants in child rehabilitation, men and women with wide vision and enthusiasm, are needed to link up the many available facilities.

Dulwich, London, S.E.19. D. F. ELLISON NASH.

NEEDS AND BEDS

SIR,—All who are aware of the compelling needs of our own grievously disabled will read with interest Miss Engberg's account of the Danish family flats (May 20), and of the Polio Research Fund's efforts to instigate similar "experiments" in this country (May 27). The most important lesson to be learnt from our Danish friends is the need for a careful preliminary inquiry into the essential requirements of each disabled person and his, or her, relatives. These vary widely, as the Danish survey shows. In England there is no lack of good will, public financial generosity, or courageous initiative, once the challenge is clear and the objective soundly based. The potential is ready to hand. For its effective deployment, we only need informed central guidance and wise coordination. We expect no less of a pioneer National Health Service.

Great Mongeham, Kent. T. TWISTINGTON HIGGINS.

SERUM-LACTIC DEHYDROGENASE IN DIAGNOSIS OF MYOCARDIAL INFARCTION

SIR,—Dr. Mellick's letter (June 3) prompts us to record that in the 18 months since the preparation of the paper [1] to which he refers, our further experience with serum glutamate-oxalacetate transaminase (S.G.O.T.) and lactate dehydrogenase (S.L.D.H.) activity in patients with myocardial infarction has been similar to his and in keeping with our original findings.

We also agree that erroneously high values for S.L.D.H. activity are obtained if appreciable hæmolysis has occurred. It can readily be calculated from the S.L.D.H. activity of whole-blood hæmolysates that approximately 15 mg. hæmoglobin per 100 ml. of serum is equivalent to the smallest increase in S.L.D.H. activity measurable by the method [2] we use. In serum having a hæmoglobin content of 15 to 20 mg. per 100 ml., hæmolysis is distinctly visible on naked-eye examination [3]; and therefore specimens with visible hæmolysis should not be used for such assays. We have not found it necessary, however, that the specimen should be freshly taken. In the absence of visible hæmolysis, no significant change occurs in the S.L.D.H. activity of serum which has been in contact with the blood-clot for several hours at room temperature.

We cannot agree with the final paragraph of Dr. Mellick's letter. The colorimetric methods we have used for the assay of S.G.O.T.[4] and S.L.D.H.[2] activities take about 90 minutes and 40 minutes, respectively, to complete, which—as we pointed out originally—is to the advantage of the S.L.D.H. test.

We find the cost of materials for these same methods is just over 1*d.* for S.G.O.T. and just under 2*d.* for S.L.D.H. assay. This includes a blank control. Material for standard curves (in duplicate) cost only 2*s.* 9½*d.* for S.G.O.T. and 4*s.* 8½*d.* for S.L.D.H.

A final point is that coenzyme I (D.P.N.) retains its stability in solution longer if it is dissolved in $\frac{M}{5}$ aqueous

1. King, J., Waind, A. P. B. *Brit. med. J.* 1960, ii, 1361.
2. King, J. *J. med. Lab. Technol.* 1959, **16**, 265.
3. Hopps, P. O. D. Personal communication.
4. King, J. *J. med. Lab. Technol.* 1960, **17**, 1.

nicotinamide instead of water. With this procedure the coenzyme solution remains stable—for purposes of the S.L.D.H. test—for at least six months at 0–4°C.

Pathology Department,
North Lonsdale Hospital,
Barrow-in-Furness,
Lancashire.

J. KING
A. P. B. WAIND.

DENTAL ANÆSTHESIA AND HYPOXIA

SIR,—I should like to thank Dr. Bourne (May 27) for pointing out once more the dangers and futility of using oxygen-restriction methods for inducing dental anæsthesia with nitrous oxide.

I have recently made a point of asking some medical and dental students from a number of schools to describe to me how they were taught to give dental anæsthetics. I was appalled to learn that out of 32 inquiries, 24 were taught to induce anæsthesia with 100% nitrous oxide. This is surely a sad reflection on our teaching and shows how old ideas die hard.

I never use less than 15% oxygen with nitrous oxide and for teaching purposes fix the lever at this setting. In children this will induce satisfactory anæsthesia within 45–75 seconds and rarely is any adjuvant required. The majority of adults can be managed in this way also but there will always be a small proportion who require an inhalational supplement if an intravenous induction has not been used. This proportion of resistant subjects will not be any less if a lower percentage of oxygen is used. I would therefore support Dr. Bourne's idea of having a fixed-percentage machine.

Royal Free Hospital.
London, W.C.1.

RONALD GREEN.

PSEUDOTUMOR CEREBRI

SIR,—There are some points of interest which I think could be usefully added to your annotation (June 10).

" Steroid Pseudotumor "

You quote Paterson and her colleagues [1] who mention associated phenomena such as premenstrual headaches, obesity, and irregular menstruation. To these should be added " menstrual red eye " [2] and premenstrual raised intraocular tension,[3] both recently reported, as they may well be further results of the same basic disturbance. Pseudotumor from prolonged steroid therapy, reported by Dees and McKay,[4] and more recently in letters in your columns,[5–9] is particularly interesting when steroids are known to reduce the cerebral œdema of allergic phenomena and also, perhaps, that of trauma.[10] Paradoxically Paterson et al.[1] report some benefit in pseudotumor from treatment with steroids. Their hypothesis that the condition is due to hyperpituitarism is attractive, but it would probably be better at the moment merely to say that it is due to steroid imbalance.

Mechanism of Pseudotumor

Smooth muscle is generally relaxed in the last few days of the menstrual cycle and during pregnancy. That the smooth muscle of the arterioles shares this relaxation is suggested by the increased bleeding found at operations performed during or immediately preceding menstruation, and by the fact that in intracranial procedures the brain at this time is often found to be swollen and engorged. It is perhaps significant that this engorgement does not appear to be affected by overventilation, which normally constricts cerebral arterioles and reduces brain bulk and bleeding.

Leaving aside the nature of the imbalance ultimately responsible, arteriolar dilatation, as suggested by Dandy and quoted by Paterson and yourselves, seems the most likely proximal cause of pseudotumor. It could also cause premenstrual headache and intracranial hypertension, and premenstrual rise in intraoccular tension and premenstrual " red eye ".

As I argued recently,[11] cerebral arteriolar dilatation will increase the amount of water that transudes from the cerebral capillary bed, and therefore increase the bulk and tension of the brain. This can happen without any increase in capillary permeability or in the venous pressure.

Respiratory Pseudotumor

Carbon-dioxide retention can produce papillœdema and a rise in intracranial pressure.[12] Paterson et al. mention this in their paper but do not discuss it. But it is interesting in this context for three reasons: (1) the proximal cause is probably the same—in this case arteriolar dilatation from a high pCO_2; (2) two causes of pseudotumor coexist when an emphysematous patient is treated with steroids; and (3) the respiratory symptoms of a person with sufficient CO_2 retention to cause papillœdema may be so slight as to be ignored by the clinician.[13]

Polycythæmic Pseudotumor

Polycythæmia per se can produce pseudotumor.[14] Again arteriolar dilatation is present, in this case because a higher pressure is needed at the arteriolar end of the capillary to force the viscous polycythæmic blood through the narrow vessel. Polycythæmia can occur as a result of steroid treatment and respiratory insufficiency. A further factor is systemic hypertension, which will of course aggravate the cerebral and ocular effects of arteriolar dilatation.

Steroid therapy, steroid imbalance, and respiratory disease can all be associated with polycythæmia and arterial hypertension. The most likely person to develop pseudotumor therefore would be an emphysematous asthmatic woman who has always had premenstrual headaches and is now being treated with steroids.

Treatment

Because a number of factors may combine to produce pseudotumor they should all be looked for and as many as possible alleviated. For instance, a fat woman with salt and water retention may well have some respiratory embarrassment. She may also be hypertensive and mildly polycythæmic. All these troubles can be treated even though we are still unable either to understand or to treat the fundamental hormonal disturbance.

Department of Neurosurgery,
Newcastle General Hospital,
Newcastle upon Tyne.

MERLIN MARSHALL.

SIR,—After your otherwise admirable annotation of June 10 on this condition, the pathology of which is so little understood, may I take you up on your nomenclature. You quote five names, four of which you imply are English, but you choose the American one.

Let me say at once that I would accept the latter if it appeared to have merit. Three of the four English terms contain the word " hydrocephalus " which you are at pains—quite correctly—to point out *never* exists in this condition. Perhaps the most repellent is " toxic hydrocephalus ", since the toxins are seldom demonstrated and the hydrocephalus is always positively shown to be absent. In fact, the absence of hydrocephalus is probably the most crucial sign which leads to the diagnosis of this disease of usually quite unknown ætiology.

Since nearly all the patients ultimately recover, the term " benign " seems reasonable. Furthermore, the evidence of intracranial hypertension (papillœdema and raised ventricular pressure) is unequivocal. It would, therefore, seem to be not

1. Paterson, R., DePasquale, N., Mann, S. *Medicine, Baltimore*, 1961, **40**, 85.
2. O'Brien, M. D. *Brit. med. J.* Feb. 4, 1961, p. 359.
3. Stephenson, R. W. *ibid.* March 4, 1961, p. 673.
4. Dees, S. C., McKay, H. W. *Pediatrics*, 1959, **23**, 1143.
5. Laurance, B. M., Matthews, W. B., Shephard, R. H. *Lancet*, 1960, i, 701.
6. Benson, P. F., Pharoah, P. O. D. *ibid.* p. 1250.
7. Warin, R. P., Evans, C. D. *ibid.* 1960, ii, 42.
8. Sneddon, I. B. *ibid.*
9. Jolly, H. *ibid.*
10. Lippert, R. G., Svien, H. J., Grindlay, J. H., Goldstein, N. P., Gastineau, C. F., *J. Neurosurg.* 1960, **17**, 583.
11. Marshall, M. *Lancet*, April 8, 1961, p. 745.
12. Conn, H. O., Dunn, J. P., Newman, H. A., Balkin, G. A. *Amer. J. Med.* 1957, **22**, 524.
13. Manfredi, F., Merwarth, C. R., Buckley, C. E., III, Sieker, H. O. *ibid.* 1961, **30**, 175.
14. Drew, J. N., Grant, F. C. *Arch. Neurol. Psychiat.* 1945, **54**, 25.

inaccurate to describe the disease as "benign intracranial hypertension" (one of the five names you mention). But it might be even better to use the term "idiopathic benign intracranial hypertension" until such time as we become more enlightened.

Sir Charles Symonds has thrown light on the ætiology of some of the cases, but in most it remains utterly obscure. If we were to insist on the prefix "idiopathic", it might act as a further stimulus to research on this puzzling disease—or, what is possibly more likely, group of diseases.

Lysholm Radiological Department,
The National Hospitals
for Nervous Diseases,
London, W.C.1. J. W. D. BULL.

EXCHANGE OF PRACTICES

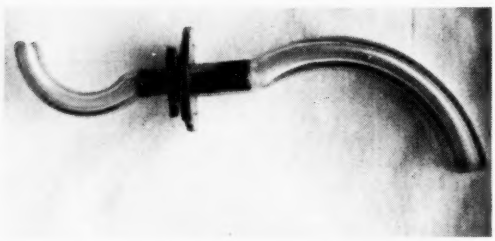
SIR,—Some months ago a doctor in the United States advertised in your columns inviting a British doctor to exchange practices with him for a short time for educational purposes.[1] By answering his advertisement I have gained a pen friend, but we cannot exchange practices because foreign doctors can obtain temporary registration in this country if they work in hospitals but not if they work in general practice.

St. Mary Cray,
Kent. E. TUCKMAN.

MOUTH-TO-MOUTH RESUSCITATION OF THE NEWBORN

SIR,—I have not seen the following method described as a means of resuscitating the apnœic newborn. It is safe, simple, and easy to carry out—for example, by a midwife on a district call.

I have modified a Safar tube; and the apparatus, which allows mouth-to-mouth breathing, consists of 2 Guedel airways (a no. 3 and no. 0) joined together, the larger being



inserted in the midwife's mouth, the smaller in the baby's mouth (see accompanying figures).

The tube is inserted after thorough clearance of the pharynx by suction. As a further precaution a catheter may be passed into the stomach to empty it and so prevent regurgitation; alternatively, or in addition, the baby may be placed in the lateral position. Using both hands to purse the baby's lips round the tube to make it airtight, the midwife then blows hard down the tube every 3 seconds. She must ensure that the baby's chest expands each time she blows. The procedure is safe; overdistension is unlikely because any excess air normally escapes through the baby's nose. Midwives here have applied this method many times safely and successfully after only brief instruction.

I wish to thank Dr. P. Toker, Sister B. A. Ratcliff, and Staff-nurse L. C. Cloete for their encouragement and help.

Boksburg-Benoni Hospital,
South Africa. N. L. WULFSOHN.

1. See *Lancet*, 1960, ii, 1248.

PSYCHIATRIC ASPECTS OF ACUTE PORPHYRIA

SIR,—Dr. Holmberg (June 3) describes a case of presumed acute porphyria in which not only did the severe depression respond to E.C.T. but the pains in the back, limbs, and abdomen disappeared as well. Dr. Holmberg says he does not mean to assert that E.C.T. has a therapeutic effect in acute porphyria but he claims that his case provides no evidence that E.C.T. will precipitate attacks of porphyria as other workers have suggested. Dr. Cashman (June 17) considers that it is the barbiturate anæsthesia which is probably responsible for exacerbations of the disorder after E.C.T. and asks whether Dr. Holmberg's patient was given E.C.T. unmodified or not.

There is no doubt that Dr. Holmberg's patient has the metabolic defect of porphyria; the diagnosis was confirmed by the finding of dark-coloured urine containing large amounts of porphobilinogen and δ-aminolævulinic acid. The question arises, however, as to whether the patient was really suffering from an acute attack of the condition. Findings recently reported by us [1] indicate that neither dark-coloured urine nor the finding of high levels of porphobilinogen and δ-aminolævulinic acid prove that an acute attack of porphyria is occurring. The excretion-rate may in fact be quite high in symptomless cases and mild attacks may be accompanied by no increase in output.

We are therefore wondering whether all the symptoms in the illness he described could not be explained on the basis of a depressive illness presenting with bodily complaints, the latter clearing up with the successful treatment of the depression.

Maudsley Hospital,
London, S.E.5. BRIAN ACKNER.
King's College Hospital,
London, S.E.5. CHARLES H. GRAY.

MALIGNANT LYMPHOMA IN AFRICAN CHILDREN

SIR,—I appreciated your interest in the lymphoma syndrome in African children to which O'Conor and I drew attention. Several of the comments, however, in your annotation of May 27, are a little misleading and tend to convey some false impressions.

It was emphasised in our paper that incidence figures could be misleading for any number of reasons, but that there could be little doubt that this disease occurred in undue frequency in certain parts of Africa. Our 106 cases from a limited population over an eight-year period compared with Roseberg's 69 in thirty years at a specialised hospital is a rather impressive comparison.

I fully appreciate, as O'Conor pointed out in the discussion of part 2 (A Pathological Entity), that all the lesions we described, with the exception of the jaw tumours, have been recorded in numerous references to lymphosarcoma, and in particular as it arises in children. Nevertheless, we felt that the consistency of the pattern clinically and pathologically in all our cases was characteristic and unique and probably of significance from an ætiological and epidemiological point of view. Continuing studies suggest some specific environmental factors, and the limits of tumour distribution appear to be possibly determined by climatic conditions suitable to certain arthropod vectors.

Finally, you seem to have invoked a peculiar licence in altering our figures for presenting sites of tumour. We did not have 26% presenting in the nasal or oral pharynx and in fact

1. Ackner, B., Cooper, J. E., Gray, C. H., Kelly, M., Nicholson, D. C. *Lancet*, June 10, 1961, p. 1256.

had none. We did, however, report 26 cases which arose in the maxilla and presented as a tumour in the mouth, not oral pharynx, as opposed to 14 which presented as exophthalmos.

It was not merely the apparently higher incidence of lymphoma in children in Africa which we wished to emphasise, but rather that the limited geographical concentration of a specific tumour syndrome having an unusually constant clinical and pathological pattern was a challenge to certain specialised disciplines in cancer research.

Mulago Hospital,
Kampala, Uganda. DENIS BURKITT.

SPIRONOLACTONE THERAPY IN HYPOKALÆMIA

SIR,—Dr. Desmit's account of the correction of hypokalæmia by an aldosterone antagonist in a six-year-old boy with an unexplained electrolyte disturbance (April 29) prompts us to report on 2 patients with cirrhosis of the liver with ascites and hypokalæmia.

We determined total exchangeable potassium (K_e) and plasma and red-cell radiorubidium 86 concentrations after giving a tracer dose of rubidium 86. These studies, which will shortly be published in detail, revealed slightly reduced total K_e (expressed in total mEq.) and accelerated build-up of red-cell rubidium 86 concentrations, which were raised.

Spironolactone ('Aldactone') therapy, 400 mg. daily for 7 days, resulted in a striking rise in K_e and in a normal distribution of rubidium between plasma and red-blood cells. Serum-potassium rose. The findings were as follows:

	Serum-potassium (mg.)	*Total exchangeable potassium (mEq.)*	*(mEq. per kg.)*
49-year-old man:			
Before spironolactone	4·2	1315	21·6
After "	4·9	2390	34·6
47-year-old woman:			
Before spironolactone	3·6	1750	27·9
After "	4·2	2460	44·4

Los Angeles County Harbor General Hospital, Torrance, California. F. K. BAUER
N. TELFER.

HISTOCHEMICAL LOCALISATION OF β-GLUCURONIDASE IN HEALING WOUNDS OF THE IGUANA

SIR,—β-glucuronidase, the enzyme related to cell proliferation and the formation of connective-tissue ground substance, has been demonstrated in the basal layers of the oral mucous membrane and the epidermis, the blood-vessels of the normal corium, and healing wounds of the skin of the back, the tongue, and the palate of the rat.[1–5]

We studied the activity of this enzyme in healing wounds of the dorsal skin and the tongue in the common iguana (*Iguana iguana*), the animals being killed after 4, 7, 14, 21, and 28 days. After excision of the wound with an extensive zone of normal neighbouring tissue and fixation in formalin/chloral hydrate, the enzymatic activity was determined by the method of Fishman and Baker [6] on frozen sections with different incubation times.

A negative reaction was found in the superficial necrotic band of the connective tissue in the 4-day specimens, whereas immediately beneath this negative zone there was an intensely positive zone due to the presence of inflammatory exudate, and particularly leucocytes. As healing progressed, the fibroblastic proliferation zone reacted moderately but consistently. The giant cells and histiocytes reacted more intensely. In the 21-day specimens the epidermis, which had proliferated over the margins of the wound, exhibited a significant increase in enzymatic activity.

In the light of these results we conclude that epithelial proliferation is closely related to β-glucuronidase activity. In connective tissue this enzyme is associated with macrophage function and tissue formation. As these results correspond with those obtained in the rat,[1–3] more extensive significance must no doubt be attached to the β-glucuronidase.

Department of Histology,
Free University, Amsterdam. A. STOLK.

1. Cabrini, R. L., Carranza, F. A. *Naturwissenschaften*, 1958, **45**, 533.
2. Cabrini, R. L., Carranza, F. A. *ibid.* 1961, **48**, 131.
3. Cabrini, R. L., Carranza, F. A. *Arch. oral Biol.* 1960, **2**, 28.
4. Seligman, A. M., Tsou, K. C., Rutenburg, S. H., Cohen, R. B. *J. Histochem. Cytochem.* 1954, **2**, 209.
5. Braun-Falco, O. *Arch. klin. exp. Derm.* 1956, **203**, 61.
6. Fishman, W. H., Baker, J. R. *J. Histochem. Cytochem.* 1956, **4**, 570.

TRANSPLANTATION OF A KIDNEY FROM AN IDENTICAL TWIN

Prof. M. F. A. WOODRUFF and Dr. J. S. ROBSON write:

"In our report on a case of kidney grafting from an identical twin (June 10) we omitted to mention that the patient had been referred to us by Dr. R. F. Robertson of Leith Hospital. Dr. Robertson had, in fact, ascertained that the patient had an identical twin, and was the first to raise the question of possible transplantation. We very much regret the omission of his name from our list of acknowledgments."

Public Health

Poliomyelitis Warning

Dr. J. A. Scott, medical officer of health for the county of London, estimates that a London child under the age of 15 who has not been vaccinated against poliomyelitis runs a risk of contracting the paralytic form of the disease 18 times greater than the child who has been vaccinated.

In an analysis of 77 confirmed cases of poliomyelitis in London last year, Dr. Scott found that of 61 persons with paralytic poliomyelitis 51 had not been vaccinated; of 16 with non-paralytic poliomyelitis 13 had not been vaccinated. In both cases, the percentage of those not vaccinated was more than 80%.

Dr. Scott estimates that by the middle of last year 70% of London children under 15 had received two injections of poliomyelitis vaccine—i.e., about 451,000 children out of a total of 644,000. Among these 451,000 there were 5 cases of paralytic poliomyelitis. Among the 193,000 who had not been vaccinated there were 39 cases.

Poliomyelitis virus was isolated from 60 cases in virological examinations in hospitals. In 27 cases the virus was of type I, and in 33 cases of type III. Type-I cases occurred throughout the year, but type-III cases were almost wholly confined to the months of July to December.

Bad Cheese

A LONDON firm of produce merchants pleaded guilty to two summonses for selling cheese unfit for human consumption.[1] At the hearing on June 16 it was stated that about 100 cases of food-poisoning among patients at Tooting Bec Hospital had been attributed to the merchants' cheese supplied to the hospital. At the West Middlesex Hospital about 30 patients and 5 staff had been similarly affected after eating cheese from the same source. Analysis showed the cheese to be heavily contaminated with streptococci.

A buyer from the firm had asked for undergrade cheese from the representatives of the New Zealand Government in Britain. He was told that New Zealand second-grade cheese was for manufacturing purposes and was sold "with all faults", a trade term, and marked W.A.F. It was said that the cheese was unsuitable for counter trade and required cooking or heat treatment.

For the merchants it was said they did not buy the cheese for manufacturing purposes; they bought only for the retail trade. "It is a fact that hospitals buy second-grade cheese and ask for second-grade cheese." The magistrate, imposing a fine of £50 in each instance, said this was a case of gross negligence.

1. *Times*, June 17, 1961.

Obituary

ARNOLD PETER MEIKLEJOHN

M.A., D.M., B.Sc. Oxon., M.R.C.P.

ON June 14 Dr. A. P. Meiklejohn, lecturer in nutrition in the University of Edinburgh, was killed by a fall from the river bank when fishing in the West of Scotland. He was 52 years of age.

He was educated at Gresham's School, Oriel College, Oxford, and St. Mary's Hospital, London. At Oxford, after taking first-class honours in physiology, he interrupted his medical studies to do research in the department of biochemistry. He played a prominent part in assisting Sir Rudolph Peters in demonstrating for the first time the enzymic role of a vitamin (thiamine) in the tissues. Soon after qualifying in 1935 Meiklejohn went to Boston with a Radcliffe travelling fellowship and later was elected Peabody fellow at Harvard University. He was one of the first to join the United Nations staff, and, as a consultant in nutrition to the European office of UNRRA, he helped to plan and carry out the programmes to relieve undernutrition in Europe after the war. In 1947 he was appointed to the department of medicine at Edinburgh University. Here his chief interests were in obesity and diabetes, and latterly in hospital catering. He was a popular lecturer and had contributed chapters on nutritional deficiency to several textbooks.

A colleague writes:

"Peter Meiklejohn had an interest in all of the many aspects of nutrition. He enjoyed his subject; appreciating good food and wine himself, he never advocated unnecessary austerities for others. He also liked good writing and he was somewhat of a perfectionist, taking endless trouble with his own papers and also with those of others, for he was much in demand as an editor. His highly developed critical faculties made him quick to detect false arguments. Working in a subject in which cranks and false enthusiasms abound, he did much to preserve the subject of nutrition as a science. He had travelled widely and had friends in many parts of the world. They will miss his wit and friendly advice, which was always freely given to his many correspondents and visitors."

Dr. Meiklejohn married Jean Campbell of Acharacle in 1954, and she survives him with two young sons.

ROBERT CECIL DAVENPORT

M.B. Lond., F.R.C.S.

Mr. R. C. Davenport, consulting surgeon to Moorfields Eye Hospital, died in London on June 17 at the age of 67.

The son of a doctor, he was born in Chungking, China. He was educated at Mill Hill School and St. Bartholomew's Hospital, qualifying in 1916. On his return from active service in the rank of captain in Mesopotamia he took the M.B. Lond. in 1920 and the F.R.C.S. the following year. His early appointments as demonstrator of physiology, house-surgeon, and ophthalmic house-surgeon at Barts were followed by a clinical assistantship at Moorfields, where he was awarded the Moorfields research scholarship. The Central London Ophthalmic and the Western Ophthalmic Hospitals shortly afterwards appointed him to their honorary staffs and in 1930 he became a member of the staff of Moorfields. Later he joined the staffs of the West London Hospital, Hammersmith, and East London Hospital for Children as ophthalmic surgeon.

At the end of the 'thirties he accepted two new responsibilities which were made heavier by wartime difficulties. In 1938 he became dean of the Moorfields school and soon afterwards ophthalmic surgeon to St. Dunstan's. In 1948 Moorfields was integrated with the Central London and Westminster Ophthalmic Hospitals, and the Institute of Ophthalmology was set up. Davenport became the first dean, and under his guidance the institute became the metropolitan centre of postgraduate ophthalmic teaching. In 1958 he was elected president of the Ophthalmological Society of the United Kingdom and the following year he retired from the office of dean.

H. E. H. writes:

"A modest man, whose work on retinal disease early established him as an authority in this sphere, Robert Davenport was distinguished by his unfailing kindliness and generosity and his unswerving integrity. His clinical interests were broad and his humanitarian instincts were never allowed to become subservient to them: to him the patient presented a human problem and never simply a technical ocular one; the student was a potential eye-doctor who must be trained and encouraged to produce his best and not simply a candidate for some suitable post.

"His appointment at St. Dunstan's was one which he valued highly, and to it, during the war years, he subordinated his other interests. The devotion which he brought to these duties is best attested by the numerous Dunstonians for whom he remained as adviser and friend long after the need for his technical ministrations had passed. It was characteristic that he should himself have begun to learn Braille in order to be able to extend his help beyond the merely technical.

"The success of the Institute of Ophthalmology must be held to be largely the result of his untiring efforts to channel through this centre the varied teachers and teaching material of the two remaining hospitals to the benefit of the large influx of home and overseas students for whom he organised the courses. Administrative skill, shrewd but kindly judgment, and enduring patience in proliferating committees were necessary to this end; but the harvest of affectionate testimonials from every part of the United Kingdom and Commonwealth which he received when he retired were a remarkable tribute to his personal qualities. Illness interrupted a well-earned, if gradual, retirement, and to the regret of many friends he was unable to be present at the celebration of the 150th anniversary of the foundation of Moorfields a few weeks ago."

Mr. Davenport married in 1928 Dr. Helen Mayfield. She survives him with two sons and a daughter.

Diary of the Week

JUNE 25 TO JULY 1

Monday, 26th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. Sodi Pallares (Mexico): New Classification of Myocardial Infarction.

UNIVERSITY COLLEGE LONDON, Gower Street, W.C.1
5 P.M. Dr. Severo Ochoa (New York): Propionic Acid Metabolism in Animal Tissues.

Tuesday, 27th

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. B. M. Ansell: Problems of Psoriasis and Arthritis.

Wednesday, 28th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Miss Jessie Dobson: John Hunter's Animals and Friends. (Arnott demonstration.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. H. J. Parish: Prevention of Tetanus.

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5 P.M. *Endocrinology.* Prof. Albert Netter (Paris): Studies upon the Stein-Leventhal Syndrome—Karyotype and Hormonal Features.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. J. O. Oliver: Bacteriology in Diseases of the Skin.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. Joseph Smart: Congenital Abnormalities of the Thoracic Cage, Lungs, and Pulmonary Arteries.

MEDICAL RESEARCH COUNCIL
5 P.M. (National Institute for Medical Research, Mill Hill, N.W.7.) Dr. Ochoa: Biosynthesis of Ribonucleic Acid.

Thursday, 29th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Dr. Pallares: Electrocardiographic Approach in Congenital Heart Disease.

ROYAL SOCIETY OF MEDICINE
5 P.M. *United Services.* Colonel J. C. Watts: Peninsular Surgeon James Guthrie.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Mr. A. K. Monro: Malignant Melanoma.

Friday, 30th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. J. A. Shepherd: Unsolved Problems in the Management of the Acute Abdomen.

Notes and News

H.M.C.s AS SPOKESMEN

Mr. Enoch Powell, Minister of Health, took team work in the hospital service as his theme when he addressed the annual conference of the Association of Hospital Management Committees on June 16. He described the members of the Association as his " eyes and ears, hands and feet " for discharging the responsibility, laid on him by Parliament, to provide a hospital service. But though " team " and " team-spirit " were nice, cosy words, easily spoken, they were not so easily realised. If the committees accepted them and really meant them, the fact must be reflected in their practical behaviour. Mr. Powell had made it clear to the regional boards that, for his part, he did mean them. Their chairmen and he met together as a team every two or three months, to discuss the major policy questions of the hospital service; their officers—secretaries, senior administrative medical officers, treasurers, and architects—formed similar teams with the corresponding officials of his department. He had made it clear to the Boards that he did not regard them as foreign bodies, on to whom he could shift responsibility, or behind whom he could shelter from criticism. On whatever lines they together administered the service, he would be proud to be their spokesman and defend and expound their actions in public and in Parliament. He agreed that to achieve the same relationship in the regions was more difficult, for the committees were numerous and varied widely in character. But these difficulties did not diminish the need to secure that, both at voluntary and official level, Board and committees felt and acted like a team. Unfortunately, in the past an H.M.C. which disagreed with a decision of its Board, about, for example, the planning of the service, had often tried to bring pressure on the Board, or perhaps on the Ministry, by making a public statement attacking the Board's decision. Nor had Boards always been slow to respond in kind, or to behave in relation to the Ministry as the management committee had behaved to them. Mr. Powell admitted that he found this " quite horrible ". The H.M.C.s had a loyalty to the Boards which should make it unthinkable that they would engage with them in public controversy. It cast the gravest slur on a service which purported to be national that those who together were providing it should squabble in public. There ought to be a practical communication and relationship between Board and committees which gave assurance that, even when a local view had not prevailed, the decision had been taken in full comradeship and understanding, not only by the Board but, where necessary, by the Minister. The H.M.C. would then be ready to defend and implement the decisions, as local spokesmen of a national service. If an individual of a committee still felt that his overriding duty was publicly to denounce what he believed to be an error, the place for him to do so was from outside, not inside, the service.

In the new long-term hospital planning operation the H.M.C.'s role as local interpreter of the new pattern of care would be especially important. Plans for the future must express the best and most progressive thinking about hospital treatment and about the share of the hospital in the whole handling of sickness. It might, for example, be found that the need for long-stay beds would be drastically reduced, or the classic figure of mental beds per 1000 population halved. The typical general hospital of the second half of the 20th century might prove to be a hospital of 400 to 800 beds, with all the main specialties, instead of the little hospitals provided with such loving care a century and more ago. To make these changes would not be easy. Old habits, traditions, prejudices, mistaken loyalties, and the pattern of administration and the complexities of salaries and gradings would add to the difficulties. But the planners had an invincible ally. The public did not want a second-rate hospital service. They wanted the most enlightened and effective handling of sickness in all its forms: they wanted modern methods, modern buildings, modern techniques, modern medicine. Let them only be convinced that these were the standards by which the plans were framed, and they would brush aside the opposition of prejudice or self-interest. Mr. Powell believed that it was to the hospital management committees, who were in direct contact with the public, that the hospital service must look to expound, as well as to implement, these changes.

SLIGHT CEREBRAL LESIONS IN CHILDREN

AT a meeting of the Association for Child Psychology and Psychiatry, held in London on June 14, Dr. H. F. R. PRECHTL (Gröningen, Holland) spoke on Children with Minimal Brain Damage.

As a result of three well-designed investigations he is convinced that very slight cerebral lesions inflicted around the time of birth have permanent sequelæ hitherto insufficiently recognised in terms of neurological, psychological, and educational difficulties. By clinical and neurophysiological examination he has recognised in schoolchildren a common syndrome marked by choreiform muscular movements and behaviour and learning difficulties. The muscular twitches, which affect mainly the proximal and facial muscles, can be identified clinically and by electromyography. Affected children tend to be hyperkinetic, and the syndrome is much commoner in boys than girls. These " choreatic " children have histories indicating difficulty in the perinatal period or maternal illness in late pregnancy. The conclusions from this retrospective investigation are validated by a further investigation in which newborns showing neurological abnormalities were followed up together with a control series. The neonatal neurological abnormalities found to be most significantly associated with later difficulties were disorders of lateralisation and tonus, hyperexcitability and diminution or absence of one or more of the normal obligatory neurological reactions. The high prognostic value of careful neurological examination of newborn infants was well illustrated in this survey.

Dr. Prechtl pointed to the difficulty of analysing the interplay of factors concerned in the association between slight brain damage at birth and the subsequent developmental problems. He had recently been interested in the effect on the mother-baby relationship of the early neurological impairment in terms of abnormal excitability, poor feeding and sleeping behaviour, and abnormalities of eye movements. An intensive follow-up study in the babies' own homes suggested that mothers with these slightly difficult and unrewarding infants had special difficulties in attaining a normal relationship with them.

University of Cambridge

On June 16 Lord Adrian opened a lecture theatre for the postgraduate medical school of the university at Addenbrooke's Hospital. The accommodation, which includes a lecture-room to seat 150 persons and rooms for the nucleus of the postgraduate medical library, has been leased to the university by the board of governors of the hospital for a peppercorn rent.

On June 10 the degree of M.D. was conferred on J. F. Watkins and of M.CHIR. on E. F. Soothill, both *by proxy*.

University of London

Prof. J. N. P. Davies, professor of pathology at Makerere College, has been appointed to the readership in morbid anatomy at the Postgraduate Medical School of London.

University of Sheffield

Dr. V. R. Pickles has been appointed reader in physiology and Mr. C. J. Dewhurst reader in obstetrics and gynæcology.

Royal College of Physicians of London

Dr. Julius H. Comroe, Jr., will give a Tudor Edwards lecture on Wednesday, July 5, at 5 P.M., at the college, Pall Mall East, S.W.1. His subject will be the pulmonary circulation and pulmonary function. The Rev. A. T. Welford will give an F. E. Williams lecture on Tuesday, July 11, at 5 P.M., at the college. He will speak on changes of performance with age.

Royal College of Surgeons in Ireland

The fellowship has been conferred on:

E. H. Chater, G. E. Edwards, T. J. M. Egan, F. G. Kenny.

Royal Society of Tropical Medicine and Hygiene

At the annual general meeting of this society, held in London on June 15, Sir William MacArthur, the retiring president, inducted as president Sir George McRobert, who presented the Chalmers medal to Dr. C. E. Gordon Smith.

Institute of Psychiatry

A symposium on the future of the mental hospitals is to be held on Oct. 5 and 6 at the institute, Maudsley Hospital, Denmark Hill, London, S.E.5. From Sept. 18 to 22 a course in practical neurochemistry is to be held at the institute. Further particulars of both these events will be found in our advertisement columns.

Royal Institute of Public Health and Hygiene

The Harben medal has been awarded to Prof. A. Bradford Hill and the Smith award to Dr. G. W. H. Townsend.

British Association of Allergists

A meeting of this Association will be held on Saturday, July 1, at 11 A.M., in the department of pathology, Tennis Court Road, Cambridge. The secretary of the Association is Dr. A. W. Frankland, Wright-Fleming Institute, St. Mary's Hospital, London, W.2.

National Association for Maternal and Child Welfare

The theme of this Association's annual conference, to be held from June 28 to 30 at Church House, Westminster, London, S.W.1, is Growing Up in the 1960s. The medical speakers will include Prof. Thomas McKeown, Dr. Margaret Manson, Dr. Elizabeth Tylden, Prof. N. F. Morris, Dr. A. J. Essex-Cater, Dr. David Lawson, Dr. P. G. Roads, and Dr. Wilfrid Warren.

Pædiatrics and Psychiatry

A meeting on this subject is to be held by the Mental Health Committee of the British Pædiatric Association, with the assistance of the Association for Child Psychology and Psychiatry, on Saturday, July 1, at 9.30 A.M., at 1, Wimpole Street, London, W.1. The medical speakers will include Prof. Douglas Hubble, Dr. David Morris, Dr. David Williamson, Dr. John Apley, Dr. Michael Balint, Dr. Mildred Creak, Dr. Ronald Mac Keith, Dr. John Bowlby, Dr. George Komrower, and Prof. Paul Polani.

West London Medico-chirurgical Society

The annual banquet was held on June 15 at the Zoological Gardens, Regent's Park.

The toast of The Society was proposed by Sir Cecil Wakeley, a member for many years, who spoke of the value of the traditions of such medical groups amid the rapid changes of the world today. In his reply, Mr. Harvey Jackson, the president, described the society's successful year, which culminates this week with Prof. A. J. Harding Rains' Simpson Smith memorial lecture on Gallstones.

Dr. W. S. C. Copeman, acting " as the local representative for Who's Who ", welcomed the guests, and particularly the presidents of five sister societies; and Dr. E. R. Cullinan, president of the Harveian Society of London, responded.

Hospital for Neurological Disorders in Cardiff

Colonel C. G. Traherne, president of the Cardiff branch of the Multiple Sclerosis Society, has officially opened Dulwich House for the board of governors of the United Cardiff Hospitals.

The building, known as the Lord Pontypridd Hospital, was formerly used for the care of children with rheumatic heart disease. In 1960, the Board agreed that it should be adapted for the care of patients with chronic neurological disorders. Extensive renovations have been made and there is now accommodation for 20 patients (10 male, 10 female). The hospital has been open since Jan. 1. The aim is to provide a centre where patients (aged between 15 and 55 years) may have long-term care under Dr. J. D. Spillane, consultant neurologist. There is a physiotherapy department, three acres of lawns and gardens, and equipment for caring for disabled patients. The hospital will provide symptomatic treatment, reablement after a first attack or relapse of multiple sclerosis, and temporary care for the seriously disabled, so that their relatives can have a rest.

Multiple Sclerosis Society

This society announces the following awards.:

Dr. R. S. Allison, Belfast.—A grant of up to £3000 towards a survey of multiple sclerosis, to be carried out in the Shetlands and Faroes during 1960–63 in collaboration with Prof. Mogens Fog and Dr. Kay Hyllested of Copenhagen.

Dr. A. M. G. Campbell, Bristol.—A grant of £1000 to Dr. Palsson (Iceland), to continue his work on sheep in connection with multiple sclerosis and Visna

Dr. J. A. R. Lenman, Dundee.—A grant of £4000 over two years for a survey of multiple sclerosis in the county of Angus.

Dr. W. H. McMenemey, London.—A grant of £1000 over two years to provide a technician for work on electrophoresis.

On June 16 Sir Selwyn Selwyn-Clarke presented the Chadwick gold medal for 1961 to Mr. E. P. Munro, executive officer, Housing and Town Planning Authority, Dominica, British West Indies.

On Wednesday, June 28, at 11.30 A.M., at the Whittington Hospital Archway Wing, London, N.19, Sir Adolphe Abrahams will give a lecture entitled Pitfalls in some Gastroenterological Symptoms.

CORRIGENDUM; *Circulating Antibodies in Reticuloses.*—We regret that in the article by Miss Mollie Barr and Dr. G. Hamilton Fairley (June 17, p. 1305) two figures were transposed: the figure shown as fig. 2 is in fact fig. 6, and that shown as fig. 6 is fig. 2.

Appointments

BANE, ADOLPH, M.B. Cape Town, F.R.F.P.S.: assistant physician (geriatrics), Nottingham City Hospital and Sherwood Hospital.
FURLONG, OLIVE C., M.B. Manc., D.C.H.: assistant county M.O., Kent (Sittingbourne area).
HOBBS, GINA L., M.R.C.S.: assistant county M.O., North West Kent area.
MOIR, A. R. M., M.D. Edin., D.P.H.: M.O.H. and principal school M.O., Stockport.
ROBERTS, DOROTHY M. H., M.B. Durh.: senior assistant M.O. (handicapped schoolchildren), Oxford.
SHANKS, H. G. I., M.B. Belf., M.R.C.O.G., F.R.C.S.E., D.OBST.: consultant obstetrician and gynæcologist, Worksop and Chesterfield areas.
SINCLAIR, JAMES, M.B. St. And.: assistant psychiatrist (S.H.M.O.), State Mental Hospital and State Institution for Mental Defectives, Carstairs, Lanarkshire.
STEVENS, J. D., M.D. Lond., M.R.C.P.: consultant chest physician, Mexborough area.
TALBOT, C. H., M.CHIR. Cantab., F.R.C.S.: consultant surgeon, United Sheffield Hospitals.
THOMAS, L. P., M.CH. Wales, F.R.C.S.: consultant surgeon, Royal Gwent Hospital, Newport.

Manchester Regional Hospital Board:

FREEMAN, H. L., B.M. Oxon., D.P.M.: consultant psychiatrist, Springfield Hospital and Salford hospital group.
GOULD, L. V., M.B. Lpool, D.M.R.D.: consultant radiologist, Salford hospital group.
JOSHI, D. M., M.B. Karachi, M.R.C.P.E., F.R.F.P.S.: assistant physician in geriatrics, Bolton and District hospital group.

South Western Regional Hospital Board:

EDWARDS, E. M., M.S. Lond., M.R.C.O.G., D.OBST.: consultant obstetrician and gynæcologist, North Gloucestershire clinical area.
MUIR, B. J., M.B. Cantab., F.F.A. R.C.S., D.A.: consultant anæsthetist, North Devon Infirmary, Barnstaple.
SKINNER, P. A., M.B. Lond., F.F.A. R.C.S.: consultant anæsthetist, Frenchay Hospital, Bristol.
WOOD, F. J. Y., M.D. Cantab., M.R.C.P.: consultant physician (geriatrics) South Somerset clinical area.

South-Eastern Regional Hospital Board, Scotland:

GOULD, JAMES, M.D. Edin.: consultant bacteriologist, Western General Hospital, Edinburgh.
HORN, D. W., M.B. Edin., D.P.H., D.T.M. & H.: M.O., headquarters staff.
MACPHERSON, A. I. S., CH.M. Edin., F.R.C.S.E.: consultant in general surgery, Edinburgh Northern hospital group, with duties at Leith Hospital.
OLIVER, M. F., M.D. Edin., F.R.C.P.E.: consultant in general medicine, Royal Infirmary, Edinburgh.
SINCLAIR, I. S. R., M.B. Edin., F.R.C.S.E.; consultant in general surgery, Royal Infirmary, Edinburgh.
SINCLAIR, KENNETH, M.B. Edin., M.R.C.P.E., M.R.C.P.: consultant physician, West Fife hospital group.

The Hospital for Sick Children, Great Ormond Street, London:

BATTERSBY, E. F., M.B. N.Z., F.F.A. R.C.S., D.A.: anæsthetic registrar.
BEILIN, L. J., M.B. Lond.: house-physician.
KASETTI, VEERANNA, M.B. Madras: resident registrar, ear, nose, and throat department.
ROLFE, MURIEL, M.B. Lond.: part-time M.O.
SCHISTAD, GUNNAR, CAND. MED. Bergen: sponsored house-surgeon.
SLACK, W. W., B.M. Oxon., F.R.C.S.: surgical outpatient assistant.

Births, Marriages, Deaths

BIRTH

CONNOR. On June 14, at Glossop Terrace Maternity Hospital, Cardiff, to Mona (née Needs) and Richard Connor—a son, Richard.

Index to 1961, Vol. I (Jan. – June) at front of 1961, pt. 1, (Jan. – Mar.